CERTIFICATE

This is to certify that this dissertation titled **'A COMPARATIVE STUDY OF SERUM ZINC LEVELS IN CHILDREN WITH FEBRILE SEIZURES AND CHILDREN WITH FEVER WITHOUT SEIZURES IN AN URBAN REFFERAL HOSPITAL'** submitted by **Dr.G.DHANA PRIYA,** to the faculty of Paediatric Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD Degree Branch VII (Paediatric Medicine), is a bonafide research work carried out by her under our direct supervision and guidance.

DEAN 8.10.14
Govt. Mohan Kumaramangalam
Medical College, Salem

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Dr.T.S. SUNDARARAJAN, M.D., D.C.H.,
Professor & HOD,
Department of Paediatric Medicine,
Govt. Mohan Kumaramangalam Medical College,
Salem.

Professor and Head
Department of Pediatrics
Govt., Mohan Kumaramangalam
Medical College & Hospital
SALEM - 636 001

ABSTRACT

BACK GROUND

Febrile seizures are the most common cause of convulsions in children. However, the exact underlying etiology and the pathophysiological mechanisms are yet to be established. Various theories have been put forward regarding the role of trace elements as predisposing factors in causing the convulsions. Among them, Zinc is the most interesting trace element whose role in diarrhea and pneumonia is well proven .This study was done to know the correlation between zinc and febrile seizures

OBJECTIVES

1) To estimate the serum levels of zinc in children with simple and complex febrile seizures and compare it with children with fever without seizures.
2) To compare the levels of zinc in simple and complex febrile seizures.

METHOD

The study was conducted in the Department of Paediatrics, GMKMCH, Salem. The study population included the children between 6 months to 6 years.

During the study period 60 consecutive children with simple febrile seizures, 40 consecutive children with complex febrile seizures and 200 consecutive children with fever without seizures formed the study group. Serum zinc levels were measured in the three groups by using the calorimetric method.

Statistical correlation was done using the software SPSS 11.5

RESULTS

The serum zinc levels were found to be low in 65% and 75% of children with simple and complex febrile seizures respectively. Only 20% of febrile children without convulsions had low zinc levels. Thus a positive correlation was found between zinc deficiency and febrile convulsions.

CONCLUSION

This study establishes a definite relationship between zinc deficiency and febrile seizures thereby substantiating zinc as an important predisposing factor in febrile seizures.

KEY WORDS: *zinc, simple febrile seizures, complex febrile convulsions, fever.*

INTRODUCTION

A Seizure can be defined as a paroxysmal time limited change in motor activity and behavior due to abnormal electrical discharges from the brain.[1]

International Classification of Epileptic Seizures[2] classified convulsions into 2 groups :

1. Complex seizures, in which one part of the cerebral hemisphere is activated resulting in focal signs and EEG changes
2. Generalized seizures where there is synchronous activation of neurons in both hemispheres.30% of children with first afebrile seizure have risk of epilepsy in later life. Febrile seizures belong to a special category.

Acute symptomatic seizures signify an underlying problem such as dyselectrolytemias or intracranial infections .the prognosis is usually good but it is determined by the underlying etiology, complications, management and the risk of future epilepsy. Unprovoked seizure is not an acute symptomatic seizure. Remote symptomatic seizure results from previous old stroke.

According to the World Health Organization (WHO) , epilepsy is a cause for more than 1% of global burden which is equivalent to breast carcinoma in females and lung cancer in males[3].

Epilepsy is a disease known to all since ancient times. An Assyrian-Babylonian text written over three millennia before describes the disease accurately, and Indian medicine too provides many details about the condition.[4] The term epilepsy is obtained from the Greek word epilamvanein which means to be seized or attacked.

Epilepsy was thought to be a ‘ sacred disease’ in the ancient times and by the fifth century BC, the world began to accept the real meaning of the disease. Ofcourse the battle between acceptance and prejudice, wisdom and ignorance, myth and science, and charlatanism and rationale is continuing even till today[5].. Hippocrates in about 400 BC postulated that epilepsy is not a religious punishment but rather a medical condition involving the brain which needed to be treated by drugs and diet.[6]

Epilepsy is not a specific disease or a single syndrome but a broad category of complex disorders arising from various abnormal brain functions that may be secondary to numerous underlying pathphysiological processes[4].

On epidemiological basis epilepsy is defined as presence of atleast 2 unprovoked seizure occurring in a time frame of less than 24 hours.

SEIZURE DIORDER is a broad term that is includes many disorders of the brain like epilepsy, febrile convulsions and even single seizures and seizures secondary to etiologies like metabolic ,infectious, hypocalcemia ,meningitis

In the paediatric age group, atleast 4-10% of have atleast 1 episode within initial 2 decades of life. The overall incidence rate is 3 %.the annual prevalence is 0.5-1%.

Infants and children are more prone to have seizures than adults. This reflects the greater neuronal excitability at certain ages as the excitatory glutamate system and inhibitory GABA system do not always balance each other. This results in a tendency to exhibit symptomatic seizures related to high fever, infections, minor asphyxia, medications, bacterial toxins and biochemical disturbances like hyponatremia, hypernatremia, hypocalcemia etc.

John HughlingsJackson[7] is a notable scientist who introduced latest concepts of epilepsy in the middle of 19th century. While other scientists of his time believed that epilepsy as due to generalized convulsions originating from medulla oblongata Hughlings Jackson proposed that there are many categories of seizures, each having their own physiological mechanisms and semiology. His theories on ‘dreamy states’ and ‘uncinate group of fits’ as focal seizures arising from discrete areas within the cortex touches present-day views of limbic seizures.

He also gave new concepts about the motor homunculus of the brain where all areas are represented and also many concepts on cerebral cortical control of voluntary function.

Febrile seizures is defined as an event in infancy or childhood usually occurring between six months to sixty months accompanied with fever but without evidence of intracranial infection or defined cause.[8]They are substantiated as the most common among the various types of seizures.

Febrile seizures occur in young children at a time in their development when seizure threshold is low. They typically occur relatively early in an infectious illness usually during the raise of temperature curve. Febrile seizures occur in common childhood infections such as infections of the respiratory system, otitis media, acute gastroenteritis, and children respond to these infections with comparably higher temperatures.

The onset of Febrile seizures generally follows a bell shaped curve. 94% occur within the first three years of age and 6% after three years of age. Approximately one half appears during second year of life with peak incidence between 18 to 22 months. Febrile seizures occurring before 6 months should raise the suspicion of serious infections like bacterial meningitis.

Genetics have a definite contribution in febrile seizures. The empiric chance after one child is affected is 10%; it rises to almost 50% if one parent had febrile convulsion.[9] However the exact mode of inheritance is not completely understood. Most studies suggest a dominant mode of inheritance with reduced penetrance. Linkage studies in various chromosomes have mapped the gene to chromosome 19p and 8q 13-21. The incidence in India varies between 3-5% [5.]Many studies show a slight male preponderance[10].

TYPES OF FEBRILE SEIZURE

A simple febrile seizure is generalized, tonic-clonic in nature ,lasts for a few seconds and rarely upto 15 minutes, is followed by a brief period of post ictal drowsiness and occurs only once in 24 hours.

A febrile convulsion is described as a complex or complicated type when the duration is more than 15 minutes, when repeated convulsions occur within 24 hours, or when focal seizure activity or focal findings are present during the post ictal period.

ROLE OF TRACE ELEMENTS IN FEBRILE SEIZURES

A number of trace elements are said to play a role in febrile convulsions by their co-enzyme activity or ability to influence ion channels and receptors. Studies have shown that iron, zinc, selenium, copper and magnesium play a significant role in febrile convulsions. Neurons rich in zinc carry the element in their synaptic vesicles. They are a special group of neurons. Zn is as a co-factor of glutamate decarboxylase which is an enzyme needed for gamma amino butyric acid synthesis in the central nervous system and reduced CSF zinc levels have also been noted in febrile convulsions.

Recent evidences indicate that zinc deficiency plays a significant role in febrile seizures. The following mechanisms can be postulated. Zinc increases storage capacity of glutamate or slows down the release rate of glutamate. Zinc increases the activity of pyridoxine needed for pyridoxine formation. Reciprocally pyridoxine increases the activity of glutamate decarboxylase which results in gamma amino butyric acid syntheses. Thus decreased zinc levels lowers GABA synthesis which would precipitate seizures.

This theory was supported by a study conducted by Ganesh et al in Chennai comparing febrile convulsions and controls which showed that in our country children with lower concentrations of zinc had more predisposition to seizures.

Therefore with regard to importance of febrile seizure and its possible association with zinc this study is been conducted to compare the serum zinc levels in children with simple and complex febrile seizures in comparison with febrile children without seizures in Government Mohan Kumaramangalam Medical College Hospital, Salem.

AIMS AND OBJECTIVES

1. To estimate the serum levels of zinc in children having simple and complex febrile seizures and compare it with febrile children without seizures.

2. To compare the levels of zinc in children with simple and complex febrile seizures.

REVIEW OF LITERATURE

HISTORY

Febrile seizures come under the category of acute symptomatic seizures. Upto the middle of the nineteenth century, they were not considered different from other seizures. It was thought that infantile convulsions were due to irritation of brain. Causes were presumed to be GI upset, teething and febrile illness. They were treated nonspecific and symptomatic management was done[11]. By the middle of the nineteenth century management was aimed at curing the underlying etiology more than just treating the symptomatology.[12]

In the latter part of the century, fever was regarded as the primary factor in producing convulsions in infants. That might have been due to the introduction of the thermometer into clinical field in that period.[13]

In the late nineteenth and twentieth centuries, and early 20th centuries, any convulsion in infants was considered dreadful which indicated poor prognosis. This was due to inability to distinguish this entity from infantile and serious causes of seizures. By the beginning of the next century, concepts that convulsions are a manifestation of the disease and not illness symptom were highlighted and hence treatment of the underlying etiology was given importance.

However only very few treatments which were available proved to be effective. In the middle of the 20th century, studies were published by Lennox[14] and Livingston[15] on febrile convulsions. These scientists suggested that a benign outcome was to be predicted in the age between 18 to 24 months, brief tonic clonic seizures , one episode, male children, and normal electroneurological findings.

Around the 1970s, 3 big population-based study demonstrated that there was only a much smaller risk for epilepsy following febrile convulsions[16,17] . All of them had similar results, and are considered as the foundation for our present understanding of febrile convulsions. The developmental quotient was unaffected, and the overall incidence of later epilepsy was relatively small (2%).[18]

TERMINOLOGY[19]

FIT

A fit is a clinical manifestation of cerebral dysrhythmia which may be convulsive as in generalized tonicclonic seizures or nonconvulsive seizures as in absence seizures.

SEIZURE

Seizure is a paroxysmal alteration in behavior due to any transient brain pathology.

CONVULSION

This term is used when a child shows a sudden episode of decerebrate posturing which is followed by clonic jerking.

EPILEPSY

Epilepsy is recurrent seizures due to repeated primary cerebral dysrhythmias.

STATUS EPILEPTICUS

A single seizure lasting for more than half hour or a series of epileptic seizure during which function is not regained between ictal events in a half hour period.

FEBRILE SEIZURES

Almost three decades ago, Livingston[20]observed that children with febrile seizures fared better than children with epileptic convulsions not triggered by fever, the prognosis was more favorable and they were more likely to be neurologically normal. Familiarity with clinical features and longtime prognosis of febrile seizures is essential in caring for affected children. Epidemiological studies have been useful in identifying features that carry adverse prognosis and these factors form the basis of proper seizure management and family counselling. Their occurrence is very common in the susceptible paediatric age group.

DEFINITION

As per “National Institute of health” a febrile seizure is “An event in infancy or childhood usually occurring between three months and five years of age associated with fever, but without evidence of intracranial infection or defined cause”[8]. This definition is useful because it emphasizes age specificity and the absence of underlying brain abnormalities. In clinical practice, “National Institute of health” definition must be interpreted with caution because intracranial infection may not be readily apparent, especially in very young infants. Moreover neurological abnormalities are also included and temperature threshold carrying seizures were not clearly defined.

DEFINITION BY ILAE

The “International League against Epilepsy” defined febrile convulsions as a event which occurs after first month of life, accompanied by fever excluding CNS infection ,in the absence of past history of seizure, which occurs in childhood after one month of age, attack associated with fever and not coming under the category of acute symptomatic seizures.[21]

PATHOPHYSIOLOGICAL MECHANISMS

Since the threshold for convulsions is significantly low in paediatric age group in the first five years of life, it is postulated as the reason for the occurrence of febrile convulsions in that period. They typically occur relatively early in an infectious illness usually during the raise phase of the temperature curve. Rectal temperature may exceed $39.2^{o}C$ and approximately one fourth of seizure occurs at temperature of greater than $40.2^{O}C$. Febrile seizures occur in common childhood infections such as respiratory tract illness, otitis media, acute gastroenteritis and children respond to these infections with comparably higher temperatures.

AGE OF ONSET

The onset of febrile seizures generally follows a bell shaped pattern. 94% occur within the first 3 years of age. Approximately one half appears during second year of life with peak incidence between 18-22 months. Febrile seizures occurring before 6 months of age should raise the suspicion of serious infections like bacterial meningitis. Febrile seizures after 6 years of age should be managed cautiously because benign causes are less common in older children.

GENETICS [1,3]

There seem to be a strong genetic predisposition for febrile convulsions. .The inheritance in families is dominant condition with variable expression and poor penetrance. A polygenic inheritance has also been identified. The genes involved in the disease remains to be identified. Linkage studies have identified FEB 1-7 genes on chromosome 8, 9, 2, 5, 6 as the causative genes implicated in this entity. Function of FEB 2 alone is known which is a sodium channel gene, SCN 1A. Thus environmental factors combined with genetic influences play the major role in determining the occurrence of convulsions.

GEOGRAPHIC DISTRIBUTION

The incidence in our country and other parts of the world varies between

- 5-10% in India
- 8% in Japan
- 0.5-1.5% in China
- 2-5 % in the United States[25]

SEX DISTRIBUTION

Many studies suggest that there is a slight male preponderance[10].

TYPES OF FEBRILE SEIZURE

A simple febrile seizure is primarily generalized, tonic clonic in nature, lasts for a maximum of 15 min, associated with fever and not recurs in 24 hours.

A febrile convulsion is defined as complex or complicated when the duration is more than 15 minutes, when repeated convulsions occur within 24 hours, or when focal seizure activity or focal findings are present during the interictal period.

PRECIPITATING FACTORS FOR FEBRILE CONVULSIONS

More often there is an underlying infectious etiology precipitating the febrile illness resulting in seizures. The organisms most commonly implicated are herpes virus 6[33], serous otitic infection of the middle ear caused by Streptococcus pneumoniae, Hib, Neisseria meningitides, flu, Shigella. In the recent era, the advent of vaccines against pneumococci, meningococci, Hib, flu have changed the clinical scenario of febrile convulsions.

CELLULAR MECHANISMS IN FEBRILE SEIZURE

The pathophysiology in febrile convulsions is not clear. There seems to be an important role for cytokines[22]. An increased susceptibility to convulsions is seen in association with specific interleukin alleles[23]. Circulating toxins, immune markers, and invasion of the CNS by microorganisms have been implicated, along with relative lack of myelination in the infant brain and increased oxygen requirement during the febrile illness.[31]

Immature thermoregulation mechanisms and only a small capacity to increase intracellular energy metabolism at increased temperatures are contributory factors.[32]

Gamma amino butyric acid is the most important chemical messenger needed for negative feedback inhibition mechanism of neuronal excitation.[35]This mediator is formed by decarboxylation of glutamate. This reaction is mediated by the enzyme glutamate decarboxylase. The metabolism of gamma aminobutyric acid is by transamination to succinic semialdehyde. This succinic semialdehyde is further converted to succinate by the Krebs cycle. This transamination is achieved by the enzyme transminase.

The derivative of pyridoxine vitamin mainly, pyridoxine phosphate acts as a cofactor for the reactions involved in the metabolism of glutamate decarboxylase and transaminase. Through the GABA transporter there occurs an active re uptake of the chemical messenger. Glycine and GABA are transported into the secretory vesicles by the vesicular transporter.

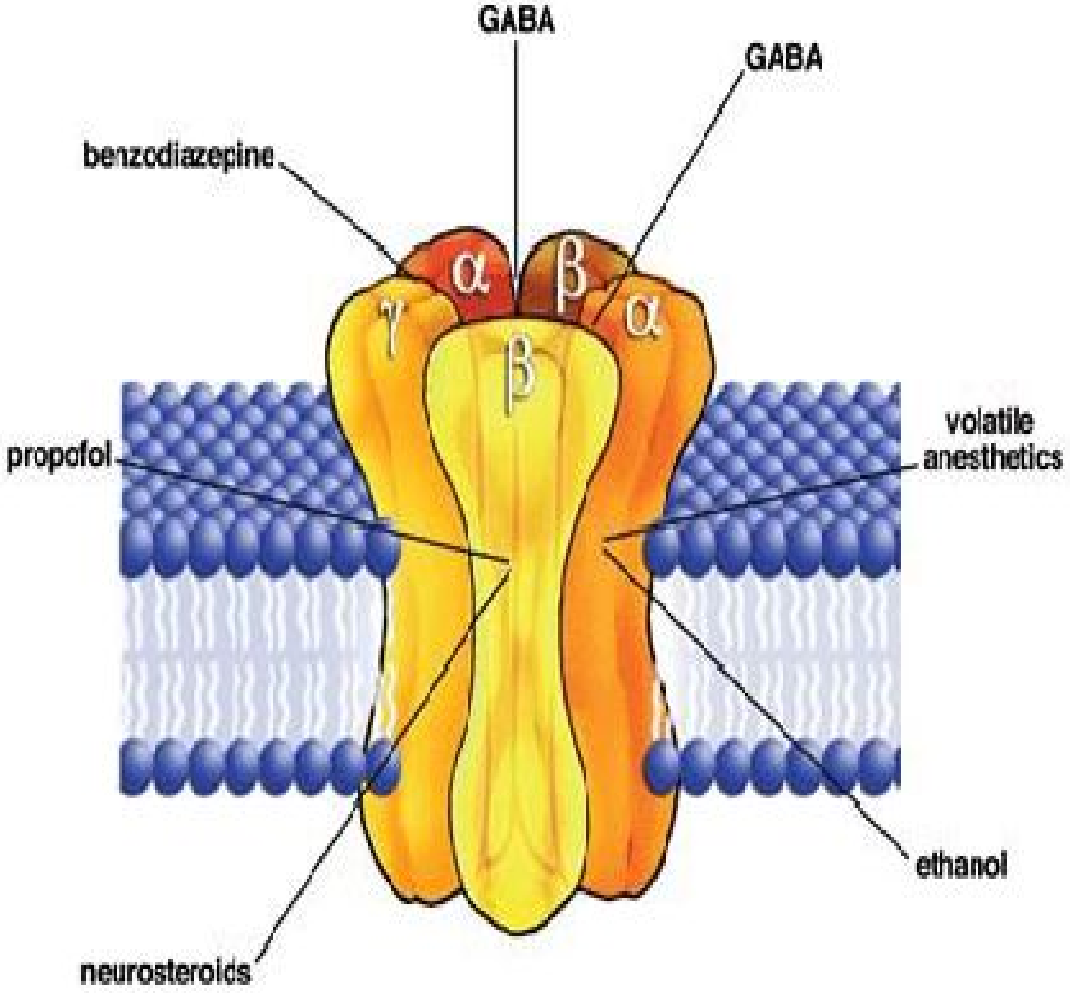
RECEPTORS FOR GABA5

3 subtypes of receptors exist. They are $GABA_A$, $GABA_B$, $GABA_C$ There is a wide distribution of $GABA_A$ and $GABA_B$ throughout the CNS while the $GABA_C$ receptors are found only in the retina. Like the nicotinic acetyl choline ligand and the glutamate ligand, the $GABA_A$ and the $GABA_C$ receptors are ion channels consisting of 5 subunits. These ion channels contain chloride ion. Whereas the $GABA_B$ receptors are bound to G-proteins increasing the conductance of potassium channels and responsible for the inhibition of adenylyl cyclase and inhibition of influx of calcium ions. This results in hyperpolarisation of neurons producing an action potential .[36,37]

Studies exhibit higher sensitization of $GABA_A$ transmembrane ligand to zinc mainly in the hippocampus and cerebellum[43,44,45]. The late inhibitory postsynaptic potential is mediated by the release of neurotransmitter from the presynaptic ends involving metabotrophic GABA B receptors. Techniques like in situ hybridization, immune histo chemistry, and ligand labeling [47]has been used to study the expression of GABA receptors in temporal lobe epilepsy .Profound changes in Ca2+ function and handling and synaptic properties have been identified, emphasizing the impairment of synaptic plasticity in hippocampal sclerosis[39].

FIG 1: GABA RECEPTOR AND THE VARIOUS SUBUNITS

THROUGH WHICH THEY ACT



Rantala et al in 1995 has reported upper respiratory infection as the triggering cause of febrile seizures in 67% of children. Other common illness associated with febrile seizures include gastroenteritis, middle ear infections and lower respiratory infections. Febrile seizures in conjunction with shigellosis constitute the most frequent extra intestinal manifestation of this infection. A direct neurotoxic effect of the Shigella bacterium on seizure also manifest with fever usually within 48 hrs of inoculation. Data from “National Collaborative Perinatal Project” indicated that the age of onset, personal and family histories and clinical presentations resemble those febrile seizures from infectious causes.

RISK FACTORS FOR RECURRENCE

The febrile convulsions have an increased chance to recur if[49,50]:

- Younger age at time of febrile seizures.
- Relatively low temperature at time of first seizure[50].
- Family history of febrile seizure in a first degree relative.
- Brief duration between fever onset and initial seizure[50].
- Multiple initial febrile seizures during the same episodes.

Age of onset is the most important predictor of febrile seizure recurrence. One half of infants younger than one year of age at the time of their first febrile seizures will have a recurrence compared with 20% of children older than 3 years.

Shorter duration of fever before the onset of convulsions and low range of temperatures are associated with increased risk of recurrence.

Febrile seizures recur in approximately 30% of those experiencing a first episode, in 50% after 2 or more episodes and in 50% of infants <1 yr old at febrile seizure onset

FEVER DURATION	RECURRENCE RATE
<1 hr	44%
1-24 hr	24%
<24 hr	13%

Table 1. Relation between duration of fever and recurrence of febrile seizures

With each 1°C rise of temperature from 101°F to 105°F, recurrence risk decreases from 35% to 13% respectively[50].

RISK FACTORS FOR OCCURRENCE OF FUTURE EPILEPSY

Data from five large cohorts indicate that epilepsy subsequently develops in 2-10% of children who experience febrile convulsions. In most studies the risk of developing epilepsy after a simple febrile seizure is not different from the common population

The several predictors of epilepsy[52] include

1. The presence of complex febrile seizures
2. Family members with epilepsy
3. Fever occurring one hour before the episode
4. Developmental delay
5. Pre existing neurological disease
6. Persistent post ictal deficit

The risk of epilepsy is highest in neurological sequelae around 28% and when several factors are combined whereas it is less than one percent in simple febrile convulsions.

FEBRILE SEIZURES- MORBIDITY AND MORTALITY[1]

There is negligible mortality in febrile convulsions. Complex seizures have an around two fold increase in long term mortality when compared with common population over the next 2 years probably due to coexisting pathology. No long term side effects have been encountered in children having more than one simple febrile convulsion. Recurrence do not cause any brain damage. These children do not have deficits in memory, intellectual function or behavior and have a normal school performance.

Status is a common neurological emergency [5] where prompt medical treatment is required to reduce the mortality and limit the morbidity that accompanies it as a result of irreversible cerebral damage.

Persistent and prolonged seizure activity cause cerebral edema, hypoxia, hyperthermia, hypoglycemia and vasomotor instability. respiratory depression may ensue from involvement of respiratory centre or from drugs used for seizure control. Vomiting and aspiration of secretions also increase morbidity. Hence treatment should be taken precedence over investigation of the cause[5].

DIFFERENTIAL DIAGNOSIS

1. Breath holding spells
2. Reflex anoxic seizure
3. Syncope
4. Rigors and Tetany.

- In breath holding spells and anoxic seizures the episodes are acute reactions to noxious stimuli, which are usually unexpected.
- Syncope is associated with limpness and bradycardia rather than tonic clonic movements and tachycardia.
- Consciousness is usually not lost in rigors and tetany.

WORK UP

A proper diagnostic work up is essential in all first episode of febrile convulsions.

The investigation panel comprises of

1. Lumbar puncture to rule out meningitis.
2. Neurological imaging studies for underlying structural abnormalities.
3. Blood investigations to diagnose etiology of convulsions.
4. Lab studies to ascertain the cause of fever.

LUMBAR PUNCTURE

The most common issue in the emergency department is whether lumbar puncture is needed. The incidence of meningitis in children with febrile seizures is between 2%-5% [57]. A diagnostic lumbar puncture is indicated if a neuroinfection is suspected or in infants experiencing the first episode within the first year. It recommended a lumbar puncture in the infant younger than 12 months of age. The child between 12 and 18 months of age, if the clinical examination is normal and history not suggestive of meningeal infection, do not require a lumbar puncture[3]. However some studies suggest that lumbar puncture is not needed in cases of initial episode of simple febrile seizure.

NEUROLOGICAL IMAGING

CT brain is not essential in the evaluation of a simple febrile convulsion. Children who experienced febrile status epilepticus have been demonstrated to have hippocampal neuronal swelling in the acute stages and later hippocampal atrophy[1].In these cases along with complex seizures require neurological imaging because they have increased risk for temporal lobe epilepsy. A study Teng et al showed presence of intracranial pathology in 4% of patients with complex febrile seizure[59]

ELECTROENCEPHALOGRAM[1]

EEG cannot predict the future occurrence of epilepsy or febrile convulsions even if the record is abnormal. Therefore it is useful only in cases where there is a greater risk for future epilepsy. Even in such cases, it is used to classify the disease more than estimating the risk of future episodes. It can also help to differentiate a prolonged post ictal period termed a nonepileptic twilight state from non convulsive status.

BLOOD INVESTIGATIONS

Blood glucose, calcium, electrolytes are not routinely indicated. Blood sugar levels are determined in children only with post ictal obtundation or poor oral intake. Complete blood count and other microbiological investigations are done to ascertain the cause of fever.

MANAGEMENT OF FEBRILE SEIZURE[1]

- History
- Exam
- Manage the acute febrile seizure and acute illness as needed
- Determine the risk factors for recurrence and estimate the risk of recurrence of febrile convulsions and later epilepsy
- Counsel the parents about the risk of recurrence and ho to provide first aid and manage fever.

TERMINATING A FEBRILE SEIZURE

Intravenous diazepam or lorazepam is the drug of choice. Rectal diazepam can also be used in a pre hospital setting and buccal or nasal midazolam spray is preferred. Intravenous benzodiazepines, Phenobarbital, phenytoin and valproate are used in cases of febrile status epilepticus[61].

PREVENTING A FEBRILE SEIZURE

ANTIPYRETICS

Aggressive treatments with antipyretics medications are carried out to bring down the levels of temperature thereby decreasing the chances of having a convulsion. However studies suggest that anti-pyretics do not reduce the chance of recurrence as seizures mostly arise in the rise or during the fall of temperatures.

ANTISEIZURE MEDICATIONS

INTERMITTENT PROPHYLAXIS[3]

Febrile convulsions are best prevented by intermittent prophylaxis with diazepam .A solution of diazepam in a dose of 0.33 mg/kg given twice to thrice daily for the first three days of fever is currently recommended. The benefit is comparable to that observed by continuous daily prophylaxis with either phenobarbitone or sodium valproate. The added advantage is reduction of side effects. Studies with oral clobazam or clonazepam have similar benefit.

CONTINUOUS PROPHYLAXIS

Phenobarbital, at a dose of 3-5 mg/kg/day achieve blood levels of 15mcg/ml which proved effective in decreasing the chances by 80%.side effects like learning disabilities and hyperactivity were encountered in almost 20% making it an unacceptable initial choice.[63]

Daily treatment with valproate (20-30 mg/kg/day in 2-3 divided doses) has also been tried. However the risk of serious hepatotoxicity especially in children below 2 years of age do not justify its use as the risk outweighs the benefit.

Phenytoin and carbamazepine are not effective in the treatment of febrile convulsions.

Continuous prophylaxis are preserved for patients[3]

- Who do not respond to intermittent prophylaxis
- Have associated intellectual disability
- Presence of family members with epileptic disorders

TRACE ELEMENTS IN FEBRILE CONVULSIONS

A number of trace elements are said to play a role in febrile convulsions by their co-enzyme activity or ability to influence ion channels and receptors. Studies have shown that iron, zinc, selenium, copper and magnesium play a significant role in febrile convulsions.

Zn^{64} acts as a co-factor of glutamate de-carboxylase, which is essential for Gamma amino butyric acid synthesis and reduced levels of the element in CSF has been observed in febrile convulsions

Copper is shown to cause seizures by causing alterations in sodium and potassium intracellular levels by inhibition of 3Na-2K ATPase channels[65].

Mg exerts its effects by altering the levels of calcim in the nerve synapses and decreasing the excitatory amino acid levels thereby preventing seizures.

Iron insufficiency is proved to play a role in the development of first febrile seizures in children. Researchers found that plasma ferritin levels where reduced in cases with febrile convulsions after comparing with children only having fever alone.[66]

ZINC

FUNDAMENTAL FACTS

Atomic weight	65
Total body zinc	35.4micromol/lit
Zinc in free fat tissues	30 microgram/g
Zinc in bones	200 microgram/g
Zinc in hair	125 to250microgram/g
Zinc in serum	60 to 110microgram/dl

Table 2: Fundamental facts of ZINC

Total body zinc is primarily intracellular thus proportional to lean body mass. The largest body stores of zinc of about 200µg/g are present in the bones. This is sequestered and does not form a part of metabolic pool.

SOURCE[67]

Zinc content of food varies widely. Very good sources of zinc are red meat and sea foods. Other good animal sources are poultry, pork and dairy products. Whole grain and vegetables represent good plant sources of zinc. Poor zinc sources are fruits and refined cereals.

Foods like potatoes, legumes have the element but the presence of substances like fiber and phytates decreases its absorption. In addition to dietary food sources, endogenous sources of zinc are pancreatic and biliary secretions released into gastrointestinal tract.

ZINC LEVELS IN VARIOUS FOODS

FOOD	ZINC LEVEL IN microgram/g
SEA FOOD	
• Oysters • Crab meat	• 17-19 • 3.8-4.3
POULTRY AND MEAT	
• Liver • Beef • Pork	• 3.1-3.9 • 3.9-4.1 • 1.6-2.1
EGG AND DAIRY PRODUCTS	
• Egg • Milk • Cheese • Legumes	• 1.1-1.3 • 0.4-0.6 • 2.8-3.2 • 0.6-1.0
GRAMS AND CEREALS	
• Rice and pasta • Bread • Vegetables • Fruits	• 0.3-0.6 • 0.6-0.8 • 0.1-0.7 • <0.1

Table 3- Food and zinc level in microgram/g.

FIG 2: FOODS RICH IN ZINC

ABSORPTION

Zinc balance is maintained by rate of absorption from the intestines and rate of excretion into intestines. Mechanism of absorption is not well understood. Zinc absorption is enhanced by glucose, lactose and soya protein. Zinc is better absorbed from human milk than cow's milk. Fiber and phytates decrease zinc absorption. Copper and cadmium compete with zinc for carrier protein. Folic acid may reduce zinc absorption when zinc intake is low. Vegetables and fruits contribute very little among the dietary sources.

REQUIREMENTS[68]

The age wise zinc requirements as suggested by the "subcommittee on the 1989, 10th edition of the RDA" are as follows:

AGE	Recommended Daily Allowance[RDA]
INFANTS	5 mg
CHILDREN	10 mg

Table-4 Age and RDA

METABOLIC ROLE OF ZINC

Zinc is an essential trace element for plants, animals, and microorganism. In human beings, zinc plays ubiquitous biological roles[69]. Zinc plays a crucial role in the functioning of about 300 enzymes. A few of zinc dependent enzymes include carbonic anhydrase, alkaline phosphatase, carboxy peptidase, superoxide dismutase, phospholipase C etc.

Zinc plays an important role in tissue or cell growth. This is related primarily to its function in the regulation of protein synthesis as well as synthesis and catabolism of nucleic acids. With respect to transcription, zinc appears to interact with nuclear proteins that bind to promoter sequences of specific genes, zinc forms a structural component of zinc fingers which recognize DNA base sequences during replication and transcription of DNA.

Zinc also regulates expression of the metallothionein gene, apoptosis and synaptic signaling.

Zinc is essential for normal function of neutrophils, natural killer cells, monocytes and macrophages.

Zinc plays an important in regeneration of intestinal mucosa, wound healing and epithelial cell turnover. These functions explain why zinc plays such an important part in the protection against infections.

ZINC AND CENTRAL NERVOUS SYSTEM

Zinc containing presynaptic vesicles was first discovered by Finn-MogensHaug in 1967. The hippocampus was found to have the highest concentration of zinc, in the brain, approximately 30µg/g dry weight.

In the CNS, zinc is found in the storage granules of the nerve synapses in a special group of neurons called zinc carrying neurons[70].

It increases the storage capacity of glutamate or slows down the release of glutamate. The element also increases the activity of pyridoxine needed for pyridoxine phosphate synthesis[71].This product catalyses the activity of glutamate decarboxylase which results in Gamma amino butyric acid synthesis. Hence decrease in zinc concentration results in lowering of GABA levels which can precipitate seizures.

Studies exhibit high sensitivity of $GABA_A$ transmembrane ligand to zinc in hippocampus and cerebellum.

LABORATORYASSESSMENT OF ZINC

Zinc is essential for growth and sexual development. It is component of many enzymes and various organs. Zinc is present as free form in 40% and bound to albumin in 60%.

Clinical features of nausea, vomiting and, metallic taste. Deficiencies are seen in sickle cell disease, acute kidney disease and drugs like steroids and oral contraceptive pills[72].

PRINCIPLE (CALORIMETRIC METHOD)

Zinc reacts with Nitro-PAPS in an alkaline medium resulting in purple coloured complex. Intensity of the colour is directly proportionate to the levels of Zinc in the sample[73,74].

$$\text{Zinc} + \text{Nitro PAPS} \xrightarrow{\text{Alkali}} \text{Purple- Colour change}$$

NORMAL REFERENCE VALUES

In the serum : 60-150 µg/dl

SENSITIVITY OF THE TEST : 96%

SPECIFICITY OF THE TEST : 92%

CONTENT	25ML	75ML
L1:Buffer reagent	20ml	60ml
L2:Colour reagent	5ml	15ml
S:Zinc standard(200ml/dl)	2ml	2ml

STORAGE / STABILITY

Serum levels are stable at temperatures of 2-8 degree celsius

REAGENT PREPARATION

They are in a ready to use form

SAMPLE MATERIAL

Serum (Free from haemolysis). Zinc is found to be unchanged in the serum for 1 week at two to eight degree celsius.

PROCEDURE

Wave length : 570nm(Hg 578nm)/Yellow

Temp : R T

Path of light : 1centimeter

Pipette into clean dry test tubes labelled as Blank (B), Standard (S) and Test (T):

TABLE 5: ADDITION SEQUENCE IN ZINC ESTIMATION

ADDITION SEQUENCE	**B**	**S**	**T**
Working reagent	1.0	1.0	1.0
Distilled water	0.05	--	--
Zinc standard(s)	--	0.05	--
Sample	--	--	0.05

Mix well and incubate at R.T. (25°C) for 5 minutes. Absorbance of the Standard (Abs. S), and Test Sample (Abs. T) is measured against the Blank, within twenty minutes.

CALCULATIONS

$$\text{Zinc in mg/dl} = \frac{\text{Abs.S}}{\text{Abs.S}} \times 200$$

LINEARITY

This procedure is found to be linear up to 700 µg/dI. If values exceed this limit, the sample has to be diluted with distilled water and the test is repeated. The accurate value is then derived using the dilution factor.

SYSTEM PARAMETERS			
Reaction	: End point	Interval	: --
Wavelength	: 578nm	Sample vol	: 0.05ml
Zero setting	: Reagent blank	Reagent vol	: 1ml
Incub.temp	: RT	Standard	: 200µg/dl
Incub.time	: 5 min	Factor	: --
Delay time	: --	Reaction slope	: Increasing
Read time	: --	Linearty	: 700µg/dl
No.of read	: --	Units	: µg/dl

TABLE 6: SYSTEM PARAMETERS USED IN ZINC ESTIMATION

Mahyar et al did a case control study at Qazvin University at Iran comparing 52 children between 9 months and 5 years with first episode of febrile convulsions with 52 healthy children in the same age group. The mean age of onset of febrile convulsions in this study was 27 months. The mean serum zinc level in the patient group was 62.8mcg/dl and in the control group was 85.7mcg/dl. The difference statistically significant indicating that hypozinconemia predisposes to febrile convulsions[75].

F. Eshanipour et al studied the serum zinc levels in three groups of children between 6 months and 5 years, group A consisted of 34 children with febrile convulsion group B consisted of 40 children with fever alone and group C consisted of 18 children with non febrile convulsions. The mean serum zinc levels of group a, group b, and group c were 76.8mcg/dl, 90.1mcg/dl and 94.5mcg/dl respectively. The serum zinc levels in febrile convulsions group were significantly lower than the other two groups. Another significant finding in this study was that children with fever had significant lower zinc levels than the children with non febrile convulsions. This study concluded that serum zinc level decreases during infection and this decrease was more significant in patients with febrile convulsions[77].

Heydarianfarhad et al did a case control study on 60 patients aged 6 months to 6 years in Iran. 30 patients had simple febrile convulsions and 30 patients had fever without convulsions. The mean serum zinc level was 66.3mcg/dl and 75.8mcg/dl in the case group and control group respectively which was statistically significant[78]

OP Mishra et al at Banaras Hindu university at Varanasi India studied CSF concentration of zinc, magnesium, copper and GABA in febrile convulsions. The study used two controls namely patients with encephalitis and patients with fever with meningismus. The mean CSF and serum zinc, magnesium, copper values were significantly decreased in febrile convulsions in comparison to other infectious encephalopathies. No significant changes were observed in serum and CSF copper levels among the three groups[82].

Palliana et al conducted a similar study at tertiary hospital in Mumbai comparing serum zinc levels of 75 children aged 6 months and 5 years admitted with first episode of febrile convulsions with that of children admitted with fever alone. The mean serum zinc level in cases and controls were 81.4mcg/dl and 90.38mcg/dl respectively which was statistically significant[80].

Mojtabaamiri et al studied serum selenium, zinc, and copper levels in children with febrile convulsions and healthy children. The mean serum zinc levels were 66.9mcg/dl and 107.8mcg/dl among cases and controls respectively. The serum selenium levels were 44.9mcg/dl and 62.8mcg/dl among cases and controls respectively. There were no difference in copper levels of two groups. This study showed that both decreased serum zinc and selenium levels play a role in febrile convulsions[81].

Ganesh et al conducted a case control study in a tertiary care hospital in Chennai consisting of 48 cases of simple febrile convulsions and 48 age matched controls (fever alone). The average zinc levels in cases and age matched controls were 33.17mcg/dl and 88 6mcg/dl respectively. This study concluded in India zinc levels were low in group of febrile convulsions. The mean age of onset of convulsions in this study was 24.8 months and no significant difference in mean zinc levels were found with respect to age, gender, and degree of temperature.[79]

METHODOLOGY

OBJECTIVES

- To estimate the levels of zinc in children with simple and complex febrile seizures for comparison with febrile children without seizures

- To compare levels of zinc in children with simple and complex febrile seizures.

MATERIALS AND METHODS

Study place	:	Department of Paediatrics, Govt. Mohan Kumaramangalam Medical College Hospital, Salem
Study subjects	:	Sample size of 300 in the three groups viz Group 1) Children with simple febrile seizures Group 2) Children with complex febrile seizures Group 3) Children with fever without seizures
Study type	:	Comparative study of zinc levels in three groups
Study period	:	6 months

Inclusion criteria

1. Children aged six months to six years with simple febrile seizures
2. Children aged six months to six years with complex febrile seizures
3. Children aged six months to six years with fever without seizure.

Exclusion criteria

The following children are excluded from the study

- Cerebral palsy
- Seizure disorder
- Chronic illness
- Dysmorphic features
- Children on zinc supplementation
- Children on anti epileptic drugs

Method

This study was conducted at GMKMCH hospital, a tertiary care teaching hospital, at Salem.

Informed consent was obtained from the parents of all the children included in the study group in a written consent form. All queries regarding the study were cleared and signature of parent was obtained. The study

protocol was approved by the ethical committee of our College on 06/12/2013.

Prior to inclusion in the study, a detailed history of presenting complaints were recorded including the duration of fever, type of seizures, duration of seizures, family history of seizures. In addition history suggestive of fever etiology cough, cold, nasal discharge, ear discharge, burning micturition or crying during micturition, breathing difficulty were also recorded.

Vitals signs namely heart rate, respiratory rate, capillary refilling time and blood pressure were recorded. The axillary temperature was recorded in all children with mercury thermometer positioned in the axilla placed for three minutes.

Anthropometric measurements namely weight, height, mid-arm circumference and head circumference were recorded for the nutritional status.

This was followed by general examination and systemic examination of the central nervous system in detail. Those children who showed features of any chronic congenital or acquired illness were excluded. Those who showed features of intracranial infection like altered sensorium, neck stiffness, bulging anterior fontanel etc were also excluded.

During the study period 60 consecutive children with simple febrile seizurs, 40 consecutive children with complex febrile seizures and 200 consecutive children with fever without seizures formed the study group. This was based on the annual morbidity pattern in our hospital.

Two milliliters of whole blood was collected by venepuncture under strict aseptic precautions and sent to biochemistry laboratory for assessment of serum zinc levels. Determination of serum zinc levels were done by calorimetric method. The principle being zinc in alkaline medium reacts with nitro PAPS to give a purple color change. Intensity of color formed depends in a direct relation to the levels of zinc found in the sample.

Though earlier studies have established a linear relationship between serum zinc and CSF zinc in children with febrile seizures, CSF zinc analysis was not done in our study and based on ethical grounds

CSF analysis was performed in all cases of febrile seizures under 1 year and in all children with complex febrile seizures. CT brain and EEG were done in cases of complex febrile seizures.

Complete blood count, urine analysis, chest X ray were done to identify the etiology of fever

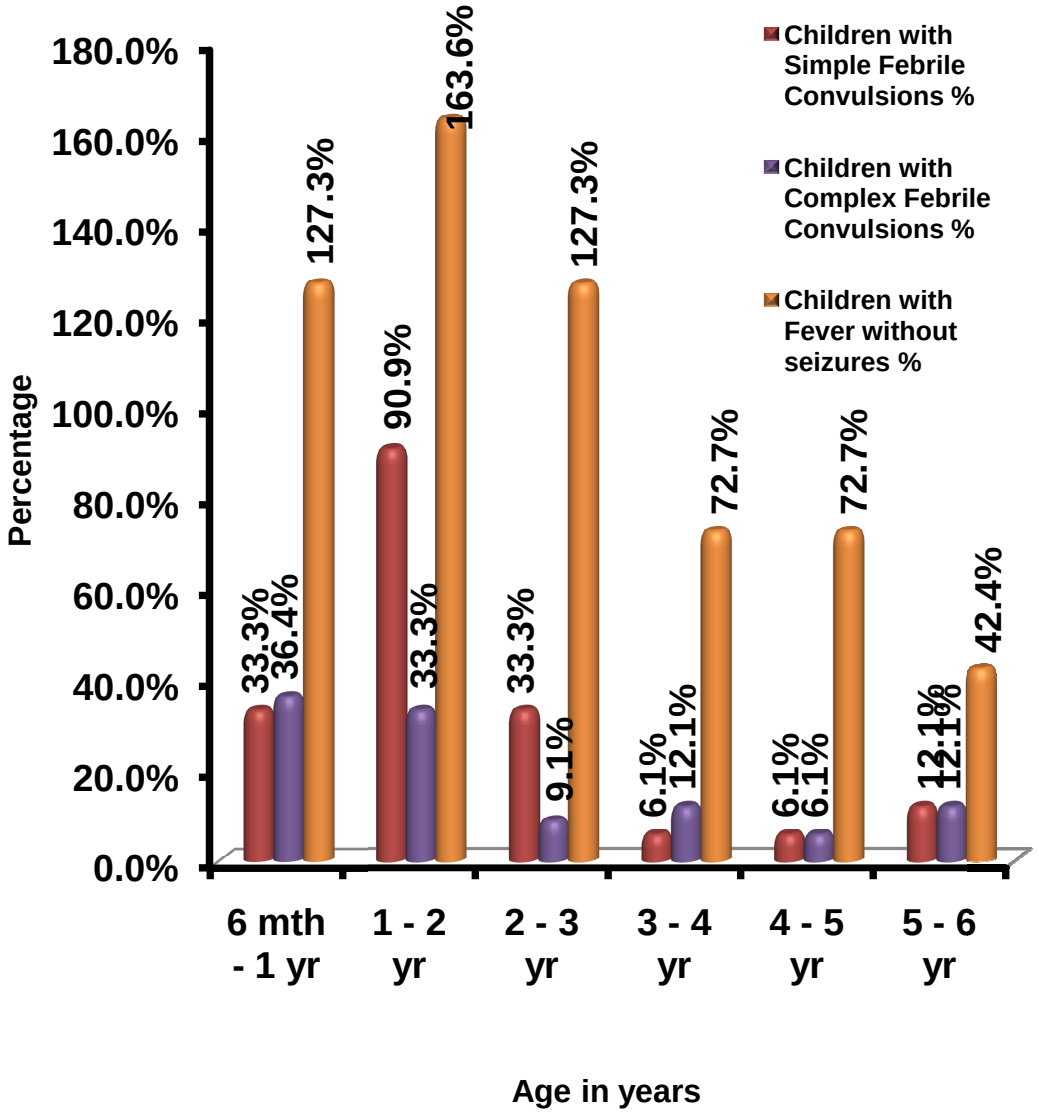
OBSERVATION AND RESULTS

AGE DISTRIBUTION:

TABLE 7 : AGE DISTRIBUTION BETWEEN THREE GROUPS

Age in years	Children with Simple Febrile Convulsions		Children with Complex Febrile Convulsions		Children with Fever without seizures	
	No	%	No	%	No	%
6 months - 1 yr	11	33.3%	12	36.4%	42	127.3%
1 - 2 yr	30	90.9%	11	33.3%	54	163.6%
2 - 3 yr	11	33.3%	3	9.1%	42	127.3%
3 - 4 yr	2	6.1%	4	12.1%	24	72.7%
4 - 5 yr	2	6.1%	2	6.1%	24	72.7%
5-6 yrs	4	12.1%	4	12.1%	14	42.4%
Total	60	181.8%	40	121.2%	200	606.1%
P - value	0.148	Chisquare				

FIG 3: DIAGRAMATIC REPRESENTATION OF AGE DISTRIBUTION BETWEEN THREE GROUPS



Majority of the children in this study are under 1-2 years of age. In simple febrile seizures and fever group whereas the majority of complex febrile cases were less than 1 year of age.

In the simple febrile convulsions group 11 of children were below 1 yr, 30 of them were between 1-2 yrs, 11 were between 2 to 3 years, 2 between 3 to 4 years and 6 of them were between 4 to 6 years of age which accounts to 33%, 70%, 33%, 6%, 6% and 12 % respectively

In the complex febrile convulsions group 12 of children were below 1years of age, 11 were between 1 to 2 years, 3 were between 2 to 3 years and 6 between 4 to 6 years of age which accounts to 36%, 30%, 9%, 12%, 6%, and 12% respectively.

In the fever group 42 of children were between 6 months - 1 yr, 54 were under 2 years of age, 42 children between 2 to 3 years, 24 were between 3 to 4 years and 24 between 4 to 5 years of age and 14 of them were between 5-6 yrs which accounts to 127%, 163%, 127%, 42%, 72% and 42% respectively.

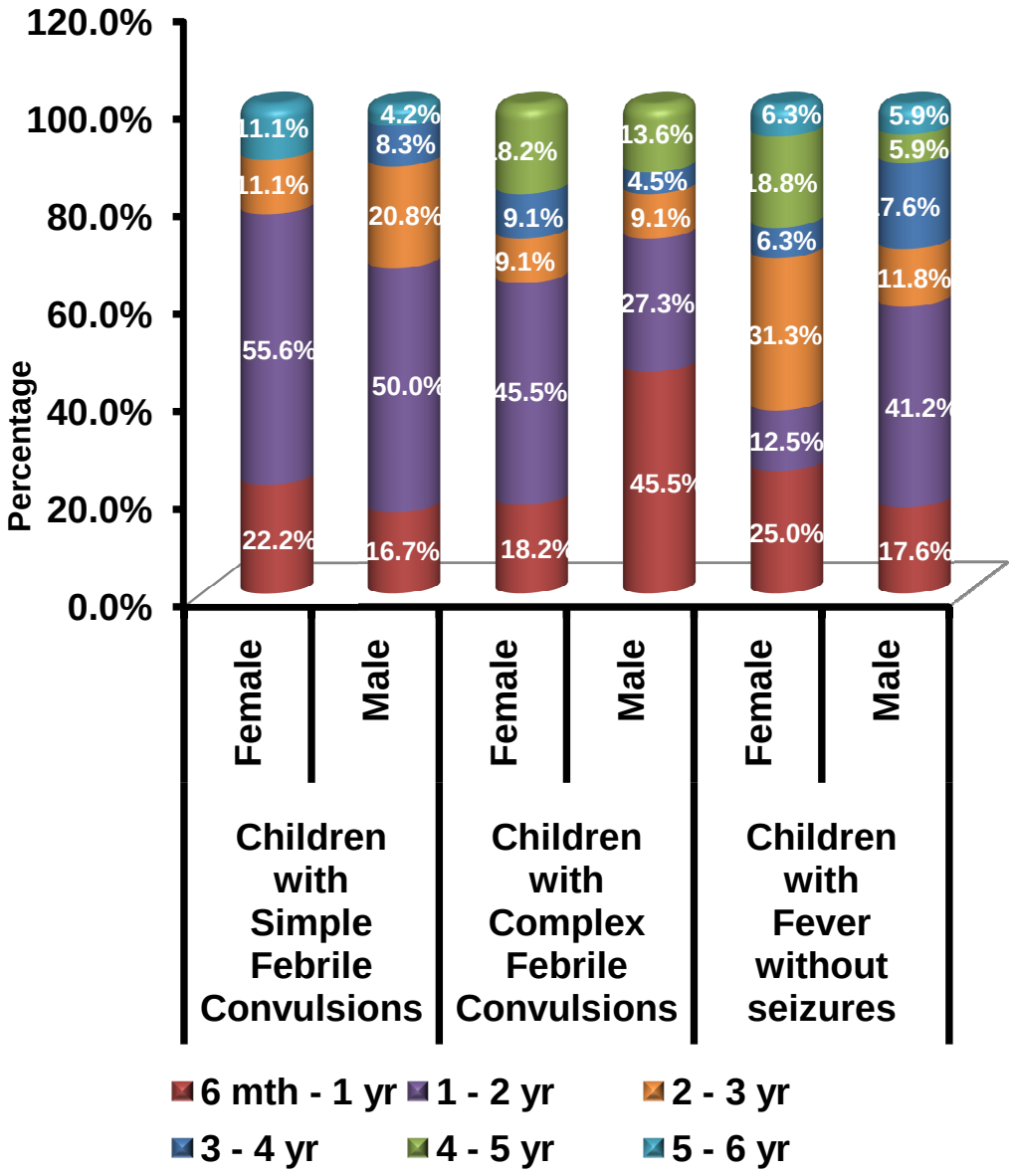
The p value shows that there is no statistically significant difference in the age distribution between the 3 groups.

TABLE 8: AGE WISE GENDER DISTRIBUTION BETWEEN THE THREE GROUPS

Age in years	Children with Simple Febrile Convulsions				Children with Complex Febrile Convulsions				Children with Fever without seizures			
	Female		Male		Female		Male		Female		Male	
	No	%	No	%	No	%	No	%	No	%	No	%
6 months - 1 yr	3	15.0%	8	20.0%	4	23.5%	8	44.4%	10	25.6%	25	15.5%
1 - 2 yr	15	75.0%	13	32.5%	7	41.2%	4	22.2%	7	17.9%	49	30.4%
2 - 3 yr	1	5.0%	10	25.0%	1	5.9%	2	11.1%	13	33.3%	29	18.0%
3 - 4 yr	1	5.0%	9	22.5%	1	5.9%	2	11.1%	2	5.1%	22	13.7%
4 - 5 yr	0	0.0%	0	0.0%	2	11.8%	0	0.0%	5	12.8%	19	11.8%
5 - 6 yr	0	0.0%	0	0.0%	2	11.8%	2	11.1%	2	5.1%	17	10.6%
Total	20	100.0%	40	100.0%	17	100.0%	18	100.0%	39	100.0%	161	100.0%

P VALUE - 0.182

FIG: 4 DIAGRAMATIC REPRESENTATION AGE WISE GENDER DISTRIBUTION BETWEEN THE THREE GROUPS



There is a female predominance only in the age group 1-2 yrs in the simple and atypical convulsions group.

In the group of children with simple febrile seizures, females are predominant among the age of 1-2 yrs whereas male children are predominant in all the other age groups.

Among the children with atypical seizures, females outnumber the males in the age group of 1-2 yrs and 4-5 yrs respectively.

In the children presenting only with fever, there is a male predominance in all the age groups.

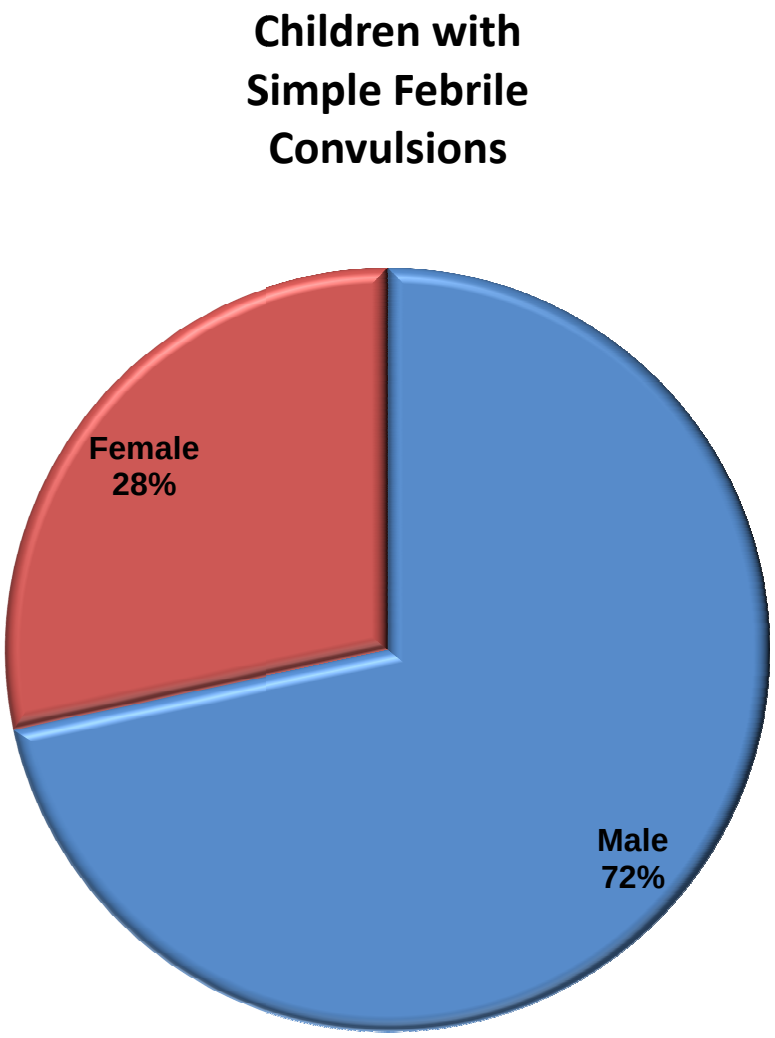
To conclude there is no statically significant difference in age wise gender distribution among the three groups.

TABLE 9: GENDER DISTRIBUTION BETWEEN THE THREE GROUPS

GENDER	Children with Simple Febrile Convulsions		Children with Complex Febrile Convulsions		Children with Fever without seizures	
	No	%	No	%	No	%
Male	43	71.7%	27	67.5%	120	60.0%
Female	17	28.3%	13	32.5%	80	40.0%
Total	60	100.0%	40	100.0%	200	100.0%

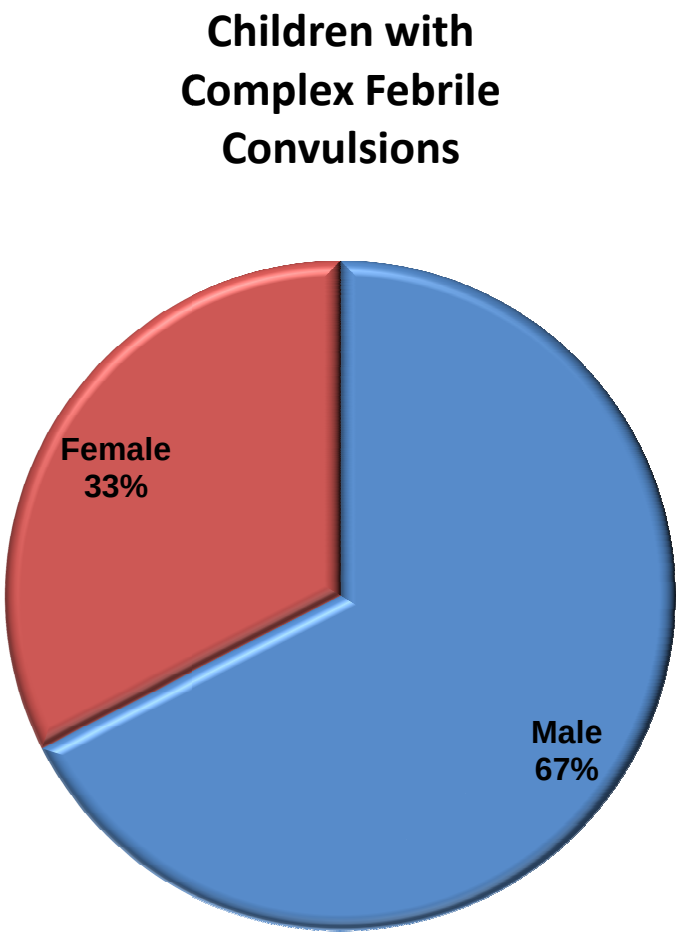
P value - 0.096

FIG 5: GENDER DISTRIBUTION IN CHILDREN WITH SIMPLE FEBRILE CONVULSIONS



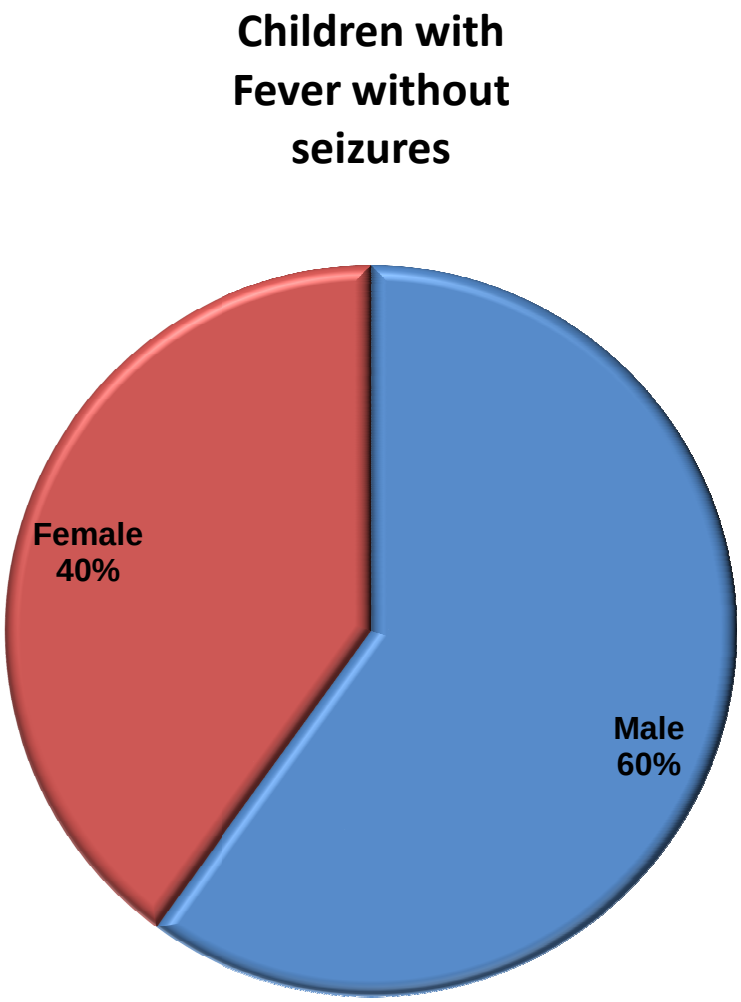
The number of female children in simple febrile seizure group are 17 and male children are 43 in number which accounts to 28% and 72% respectively.

FIG 6: GENDER DISTRIBUTION IN CHILDREN WITH COMPLEX FEBRILE SEIZURES



In the atypical febrile seizure group there are 27 males and 13 female children accounting to 67% and 33% respectively.

FIG 7: GENDER DISTRIBUTION IN CHILDREN WITH FEVER WITHOUT SEIZURES



Among the children presenting only with fever, there were 120 males and 80 females attributing to 60% and 40% respectively

There is a statistically significant difference in gender distribution among the three groups with a p value of 0.096.

There is a male predominance among all the 3 groups in this study.

The male –female ratio is 1.7:1

FOCUS OF INFECTION:

Table 10: Focus of infection

Cause	Children with Simple Febrile Convulsions		Children with Complex Febrile Convulsions		Children with Fever without seizures		P-value
	No	%	No	%	No	%	
AGE	8	13.3%	0	0%	0	0%	0.015*
AOM	5	8.3%	4	10.0%	0	0%	0.203
ENTERIC FEVER	0	0%	0	0%	26	13.0%	0.015*
LRI	2	3.3%	7	17.5%	36	18.0%	0.109
MALARIA	0	0%	0	0%	6	3.0%	0.370
PHARYNGITIS	0	0%	0	0%	18	9.0%	0.045*
URI	23	38.3%	18	45.0%	24	12.0%	0.009*
UTI	9	15.0%	4	10.0%	30	15.0%	0.702
VIRAL FEVER	13	21.7%	7	17.5%	60	30.0%	0.479
Total	60	100.0%	40	100.0%	200	100.0%	

There is a statically significant difference in the distribution of upper respiratory illness as the cause of fever among the children with simple and complex febrile convulsions. Viral fever predominates in the children only with fever.

The percentage of distribution of URI is 38.2%, 45.3% and 12% among the simple, complex febrile convulsions and only fever group respectively accounts to 23, 18 and 24 cases respectively.

Viral fever was the second most common cause of illness among the convulsions groups seen in 20.6%, 17.2% and 30.6% is seen in the only fever group which accounts to 13, 7 and 60 cases respectively.

Acute gastroenteritis is seen in 11.8% i.e., 8 cases in category of simple febrile convulsions and enteric fever is seen in 11.1% of cases in the only fever group which accounts to 30 cases

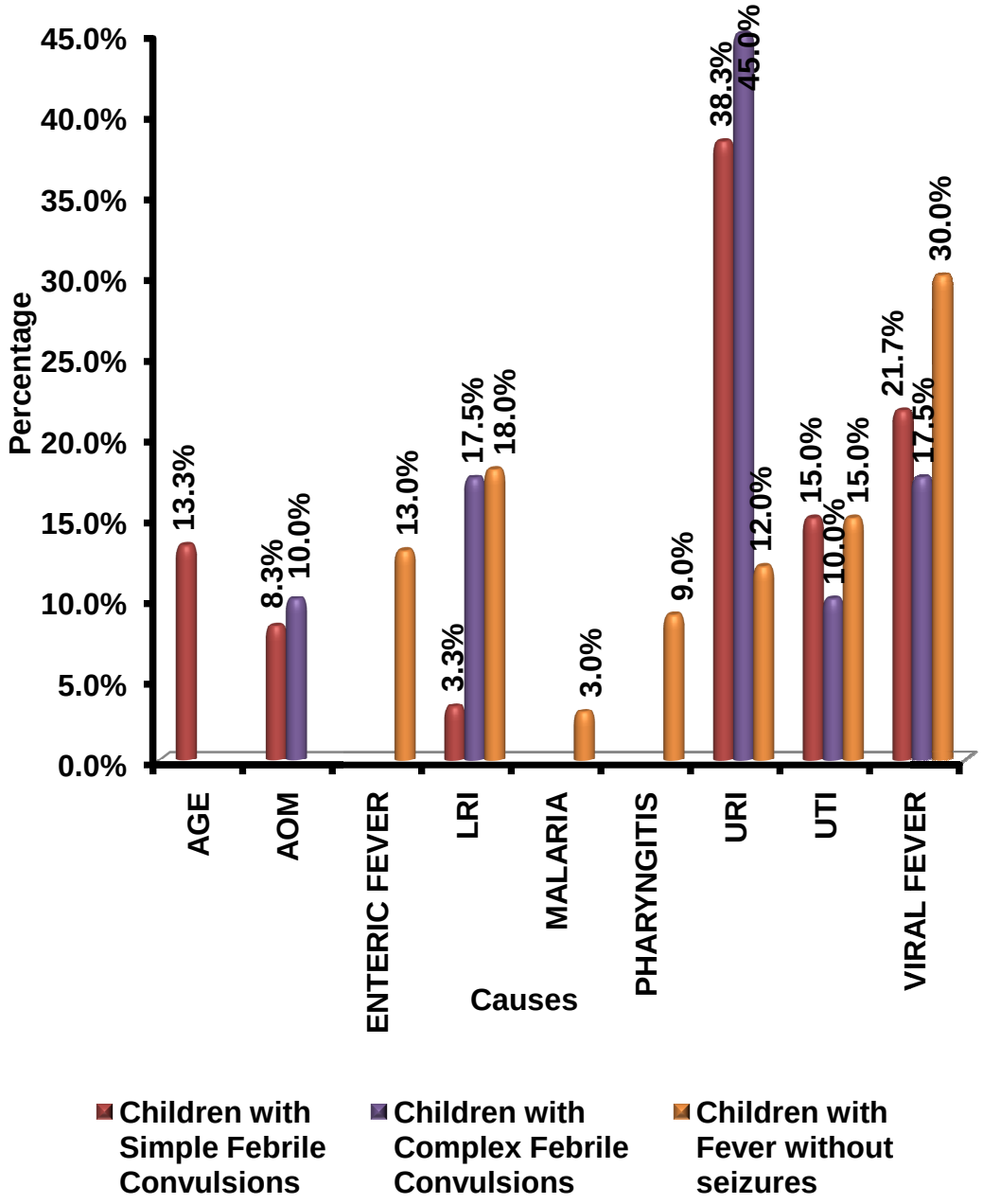
The percentage of acute otitis media in the 3 groups are 8.8%, 6.9% and 2.8% involving 5 and 4 children respectively

LRI is found in 5.9%, 17.2% and 16.7% respectively among the 3 groups as the cause of fever accounting to 2, 7 and 36 cases respectively

Malaria and pharyngitis was diagnosed in 2.8%, 6 cases and 8.3% i.e., 18 of children who presented only with fever.

Urinary tract infection was the etiology of fever in 14.7%, 10.3% and 13.9% of children accounting to 9,4 and 30 cases respectively.

FIG 8: DISTRIBUTION OF CAUSES BETWEEN THE THREE GROUPS



Upper respiratory tract infection was found to be the most common triggering illness for simple and complex febrile convulsions and viral fever predominated in the fever alone group.

FAMILY HISTORY

TABLE 11: FAMILY HISTORY IN THE CHILDREN WITH CONVULSIONS

Family history	Children with Simple Febrile Convulsions	Children with Complex Febrile Convulsions	Children with Fever without seizures	P-value
Yes	15	6	0	0.042*
No	35	34	0	

There were 15 children with positive family history among children with simple febrile convulsions and 6 children in the atypical seizure group had family history of seizures.

FIG 9: DIAGRAMATIC REPRESENTATION OF PERCENTAGE OF CHILDREN HAVING POSITIVE FAMILY HISTORY OF CONVULSIONS

Family histories of febrile convulsions were positive in 18 % of children with simple and 15% of children with complex febrile convulsions respectively.

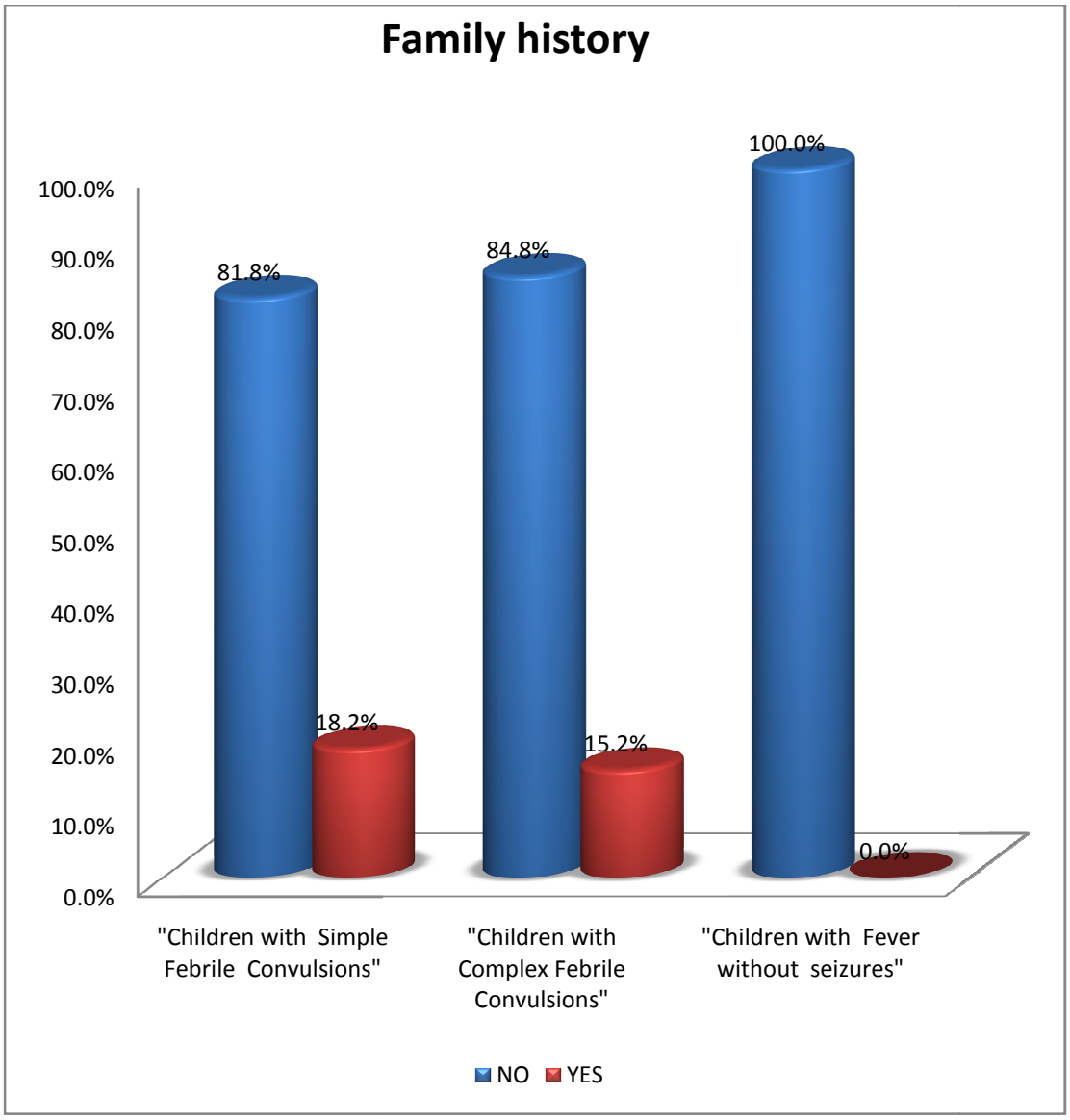
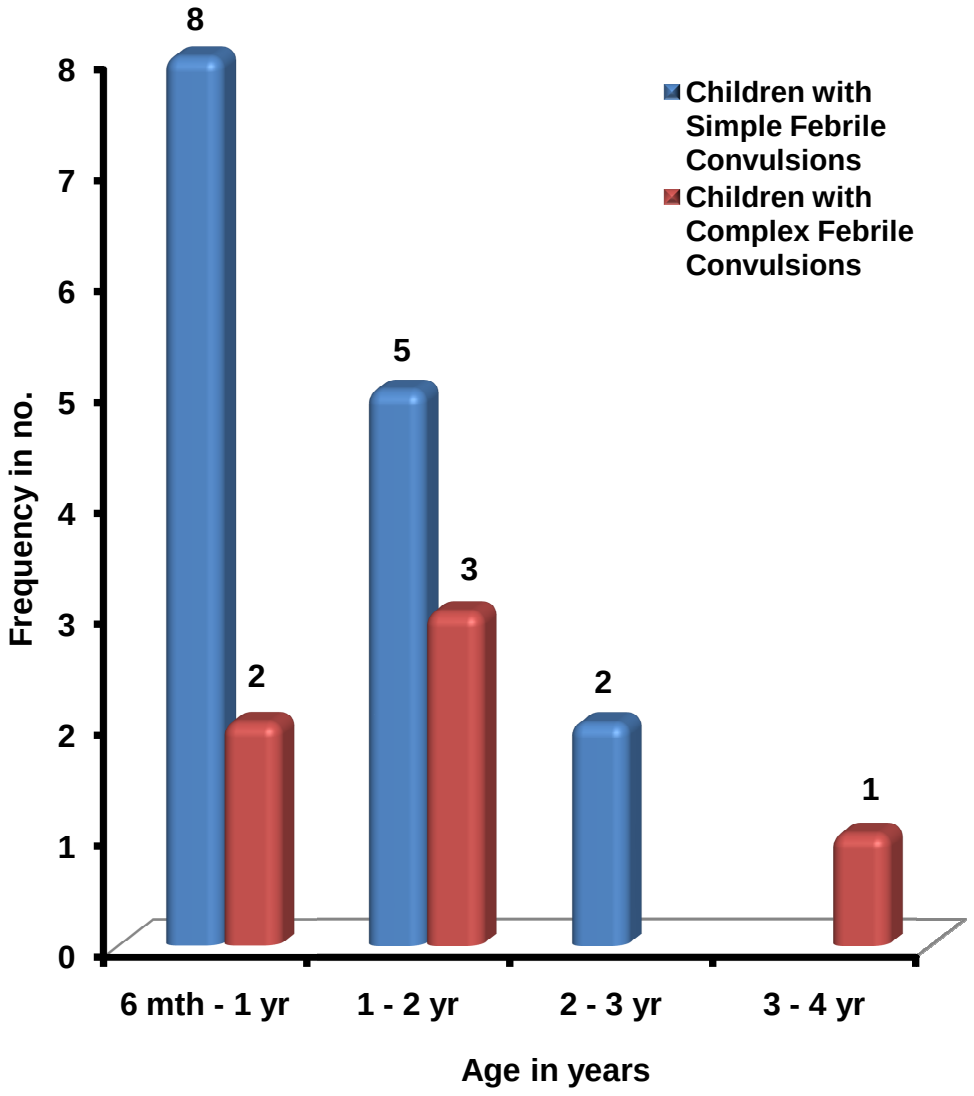


TABLE 12: AGE WISE DISTRIBUTION OF CHILDREN WITH POSITIVE FAMILY HISTORY OF SEIZURES

More than 95% of the children with positive family history were below 2 years of age.

Age group	Children with Simple Febrile Convulsions	Children with Complex Febrile Convulsions
6 months - 1 yr	8	2
1 - 2 yr	5	3
2 - 3 yr	2	0
3 - 4 yr	0	1

FIG 10: GRAPHICAL REPRESENTATION OF AGE WISE DISTRIBUTION OF CHILDREN WITH FAMILY HISTORY OF CONVULSIONS



In the children with positive family history,8 children were below the age of 1 year,5 were between 1-2 year, and 2 of cases were between 2-3 years in the simple febrile convulsions group.

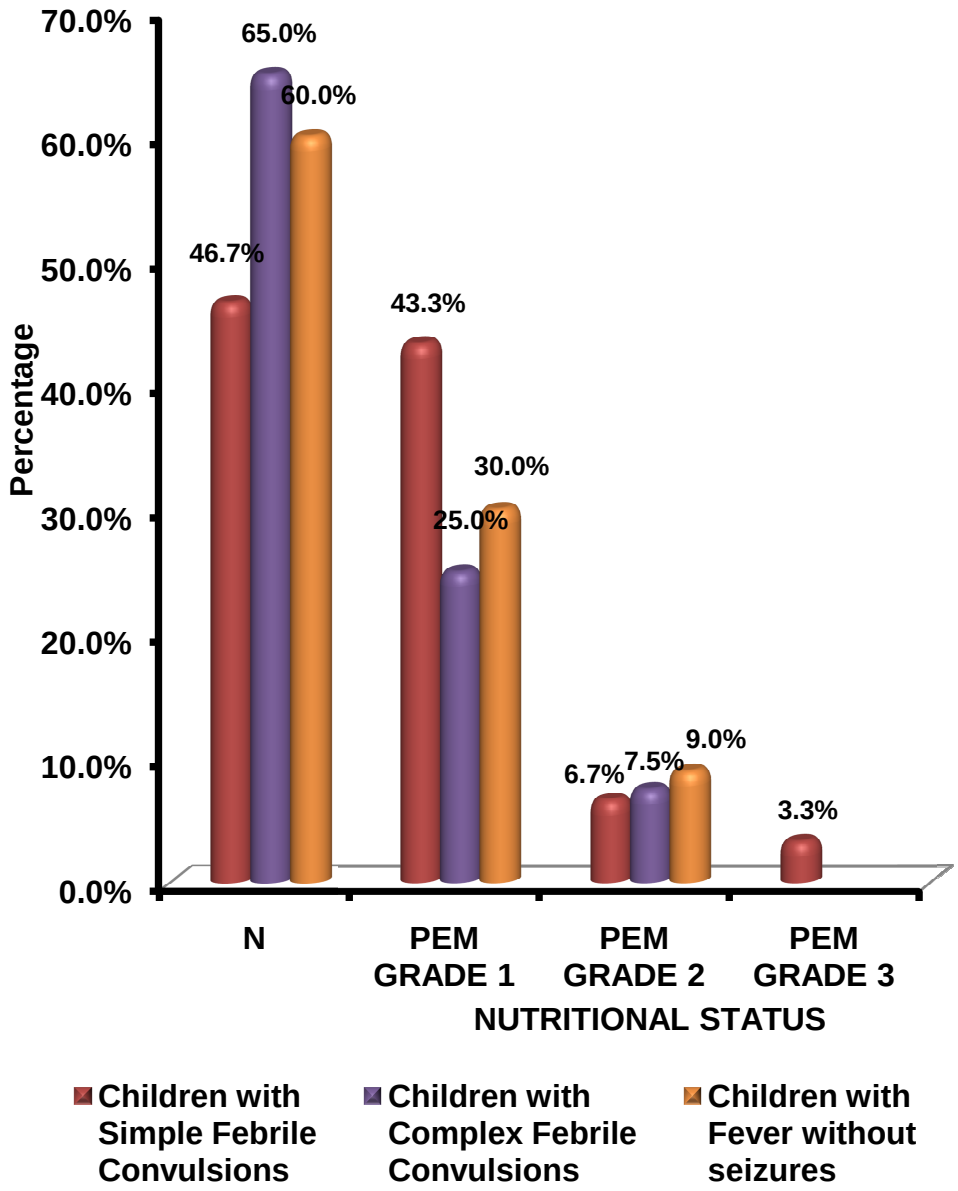
In the complex febrile convulsions, 2 were under 1 year, 3 children were between 1-2 years and 1 child was between 3-4 years

COMPARISON OF NUTRITIONAL STATUS BETWEEN THREE GROUPS

TABLE 13: NUTRITIONAL STATUS BETWEEN THREE GROUPS

NUTRITIONAL STATUS	Children with Simple Febrile Convulsions		Children with Complex Febrile Convulsions		Children with Fever without seizures		P-value
	No	%	No	%	No	%	
N	28	46.7%	26	65.0%	120	60.0%	0.307
PEM GRADE 1	26	43.3%	10	25.0%	60	30.0%	
PEM GRADE 2	4	6.7%	3	7.5%	18	9.0%	
PEM GRADE 3	2	3.3%	1	0%	2	0%	
Total	60	100.0%	40	100.0%	200	100.0%	

FIG 11: NUTRITIONAL STATUS BETWEEN THE THREE GROUPS



53% of cases with simple febrile seizures, 35% of children with complex febrile seizures and 40% of febrile children without seizures have protein energy malnutrition

Among the children having simple febrile seizures, 26 had grade 1 protein energy malnutrition,4 had grade 2 PEM, 2 of the cases had grade 3 PEM and 28 of them had normal nutritional status accounting to 43.3%, 6.7%, 3.3% and 46.7% respectively.

In the children with atypical convulsions, 10 had grade 1 malnutrition, 3 cases had grade 2 PEM, 1 child had grade 3 PEM and 26 cases had normal nutritional status with the percentage attribution of 25%, 7.5% and o% and 65% respectively.

In the fever alone group,60 cases had grade 1 malnutrition, 18 children had grade 2 PEM, 2 of them had grade 3 PEM and 120 had normal nutritional status which accounts to 30%, 9% and 60% respectively.

There is no significant difference in the nutritional status among the children in the 3 groups.

TABLE 14: COMPARISON OF GENDER WISE NUTRITIONAL STATUS IN THE CHILDREN BETWEEN THE THREE GROUPS

Nutritional status	Children with Simple Febrile Convulsions				Children with Complex Febrile Convulsions				Children with Fever without seizures			
	Female		Male		Female		Male		Female		Male	
	No	%	No	%	No	%	No	%	No	%	No	%
Normal	4	22.2%	25	58.3%	5	36.4%	20	74.1%	40	50.0%	84	66.1%
PEM 1	11	66.7%	12	33.3%	6	46.2%	6	22.2%	24	30.0%	36	28.3%
PEM 2	2	11.8%	3	7.0%	2	18.2%	1	3.7%	16	20.0%	5	3.9%
PEM 3	0	0.0%	3	7.0%	0	0.0%	0	0.0%	0	0.0%	2	1.6%
Total	17	100.%	43	100.0%	13	100.%	27	100.%	80	100.%	127	100.%

Among the females, 11 and 2 children had grade 1 and grade 2 PEM in the group with simple febrile seizures accounting to 66% and 11%.

In the atypical convulsions group, 6 (45%) and 2 cases(18%) had grade 1 and grade 2 protein energy malnutrition among the females

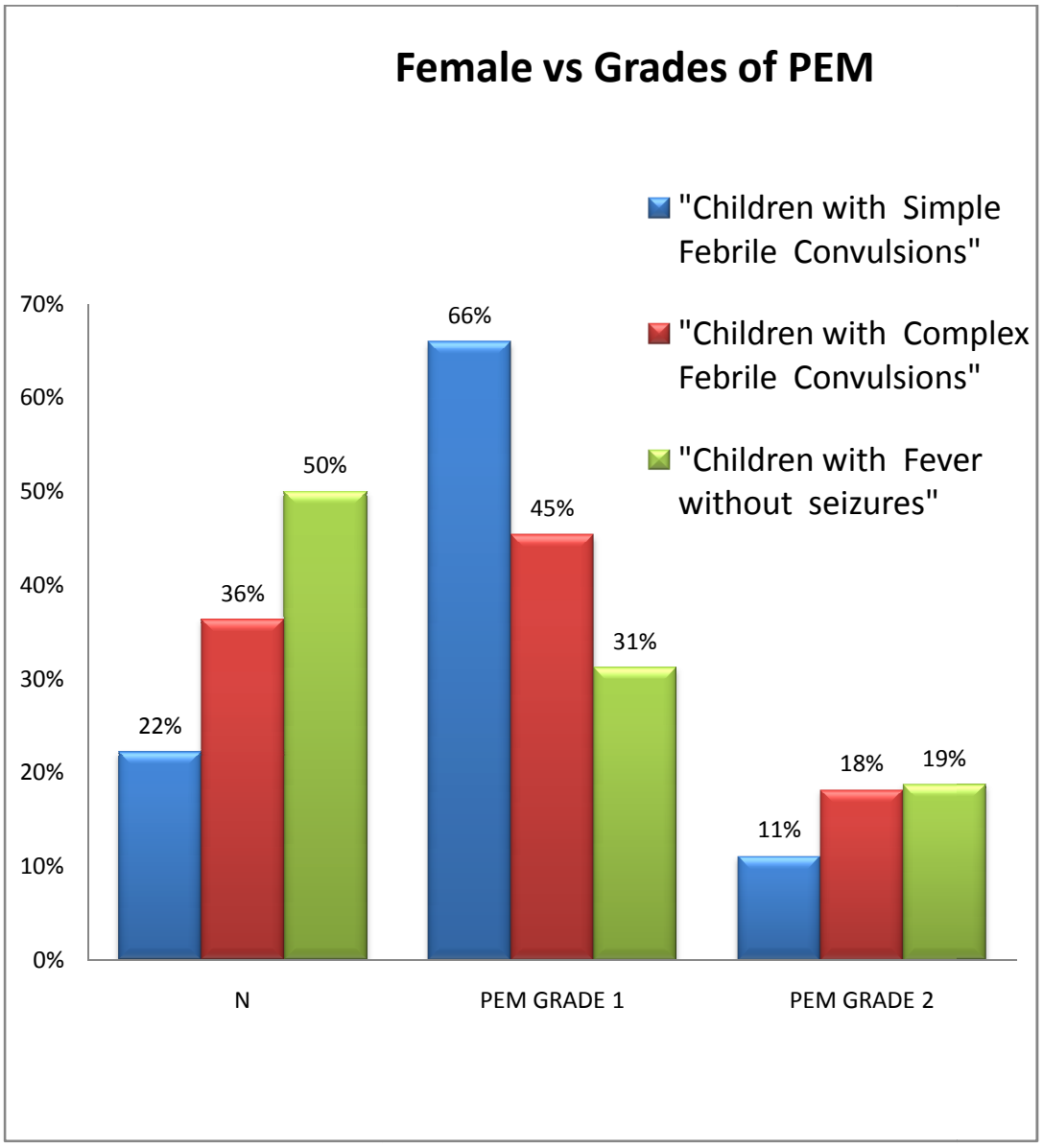
In the febrile group, 41 and 20 cases had grade 1 and 2 PEM accounting to percentages of 44% and 16% respectively.

Among the male children, 12, 6 and 36 had grade 1 PEM in the respective 3 groups accounting to 33%, 18% and 29%.

In the male children with grade 2 PEM, 3, 1, and 5 cases belong to the 3 groups accounting to 6%, 5% and 4% respectively.

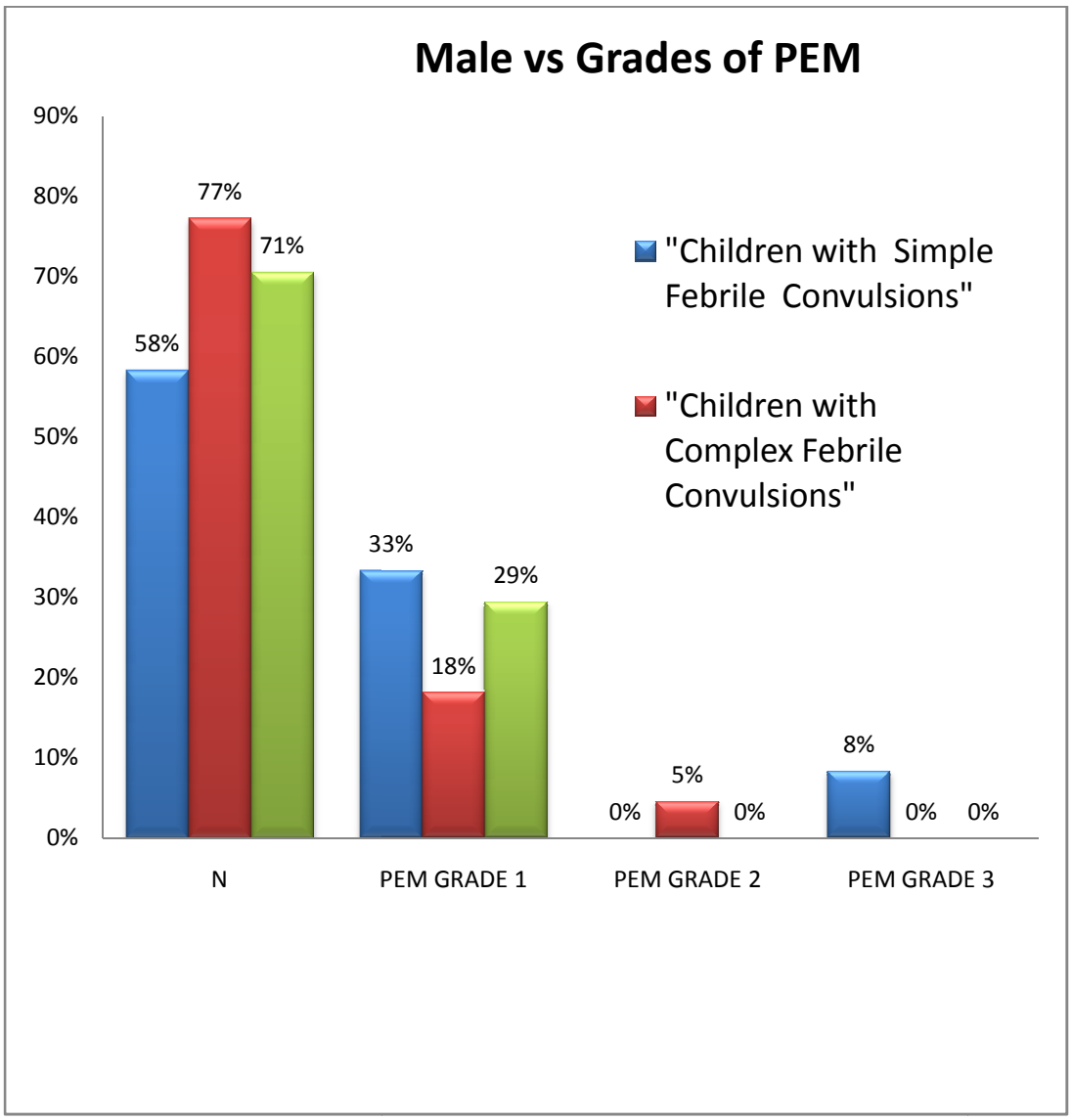
Grade 3 PEM as seen in 3 (8%) cases in the male children with simple febrile seizures and 2(1%) males in the only fever group.

FIG 12: FEMALE CHILDREN VS GRADES OF PROTEIN ENERGY MALNUTRITION [PEM]



In the simple and complex febrile convulsions group, females predominately had grade 1 protein energy malnutrition accounting to 66% of cases. In children having only fever, 50% had normal nutritional status.

FIG 13: MALE CHILDREN VS GRADES OF PEM



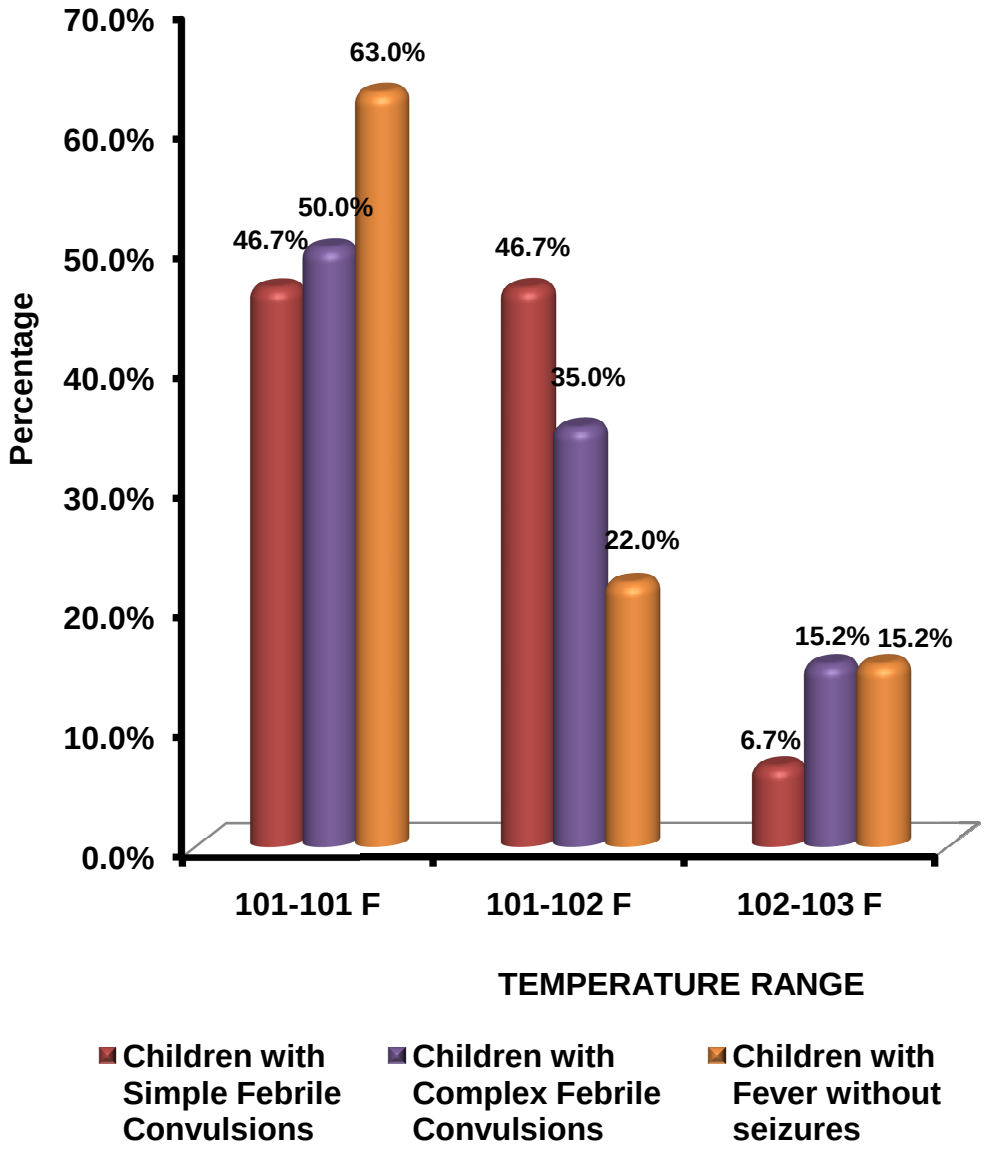
The males predominately had normal nutritional status followed by grade 1 PEM in all the 3 groups.

RANGE OF TEMPERATURE IN THE THREE GROUPS:

TABLE 15: RANGE OF TEMPERATURE BETWEEN 3 GROUPS

TEMPERATURE RANGE	Children with Simple Febrile Convulsions		Children with Complex Febrile Convulsions		Children with Fever without seizures		P-value
	No	%	No	%	No	%	
100-100.9 F	28	46.7%	20	50.0%	126	63.0%	0.307
101-101.9 F	28	46.7%	14	35.0%	44	22.0%	
102-103 F	4	6.7%	6	15.2%	30	15.2%	
Total	60	100.0%	40	100.0%	200	100.0%	

FIG 14: RANGE OF TEMPERATURE BETWEEN THREE GROUPS



Majority of the children recorded temperature between 100-100.9 Farenheit.

In the group of simple febrile convulsions, 28 had 100-100.9., 28 cases had 101-101.9 F and 4 children had 102-103 accounting to 45%, 48% and 6% respectively.

In the atypical convulsions group, 20, 14 and 6 children had temperature ranges of 100-100.9., 101-101.9 and 102-103 accounting to 51%., 33% and 15% respectively.

In the fever group, 126, 44 and 30 children recorded the respective temperatures attributing to 63%, 21% and 15% .

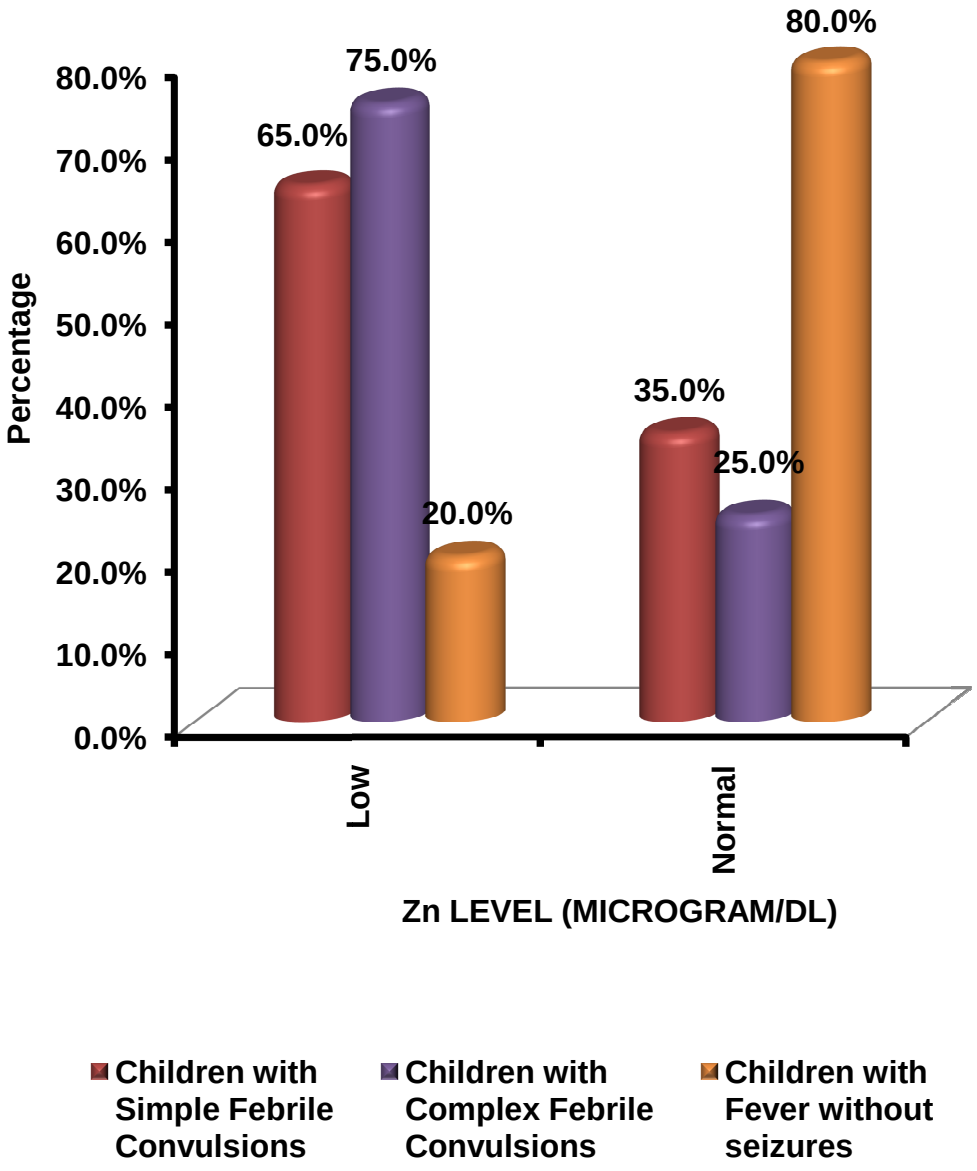
From the above table, it is evident that the children with lower zinc levels are more prone to develop febrile seizures even at lower temperature ranges.

SERUM ZINC LEVELS IN ALL THE THREE GROUPS:

TABLE 16: ZINC LEVELS IN CHILDREN STUDIED

Zn LEVEL (MICROGRAM/ DL)	Children with Simple Febrile Convulsions		Children with Complex Febrile Convulsions		Children with Fever without seizures		P-value
	No	%	No	%	No	%	
Low	39	65.0%	30	75.0%	40	20.0%	0.002**
Normal	21	35.0%	10	25.0%	160	80.0%	
Total	60	100.0%	40	100.0%	200	100.0%	
Mean ± SD	57.69 ± 9.46		60.66 ± 11.33		73.12 ± 15.15		

FIG 15: DIAGRAMATIC REPRESENTATION OF THE SERUM ZINC LEVELS IN THE THREE GROUPS



Mean ZINC levels are significantly less in Children with Complex febrile convulsions followed by Children with Simple febrile Convulsions

Correlation between the zinc and the 3 study groups:

1) Simple febrile vs fever without seizures P<0.002(significant)
2) Complex febrile vs fever without seizures P<0.002(significant)
3) Simple febrile vs complex febrile P=0.700(not significant)

Normal reference range of zinc values: 60-150 microgram/dl

Serum zinc levels were found to be low in 39 children in simple febrile seizures which accounts to 65%

Serum zinc levels were found to be low in 30 children in complex febrile seizures that accounts to 75%

Serum zinc levels were found to be low in 40 febrile children without seizures accounting to 20%

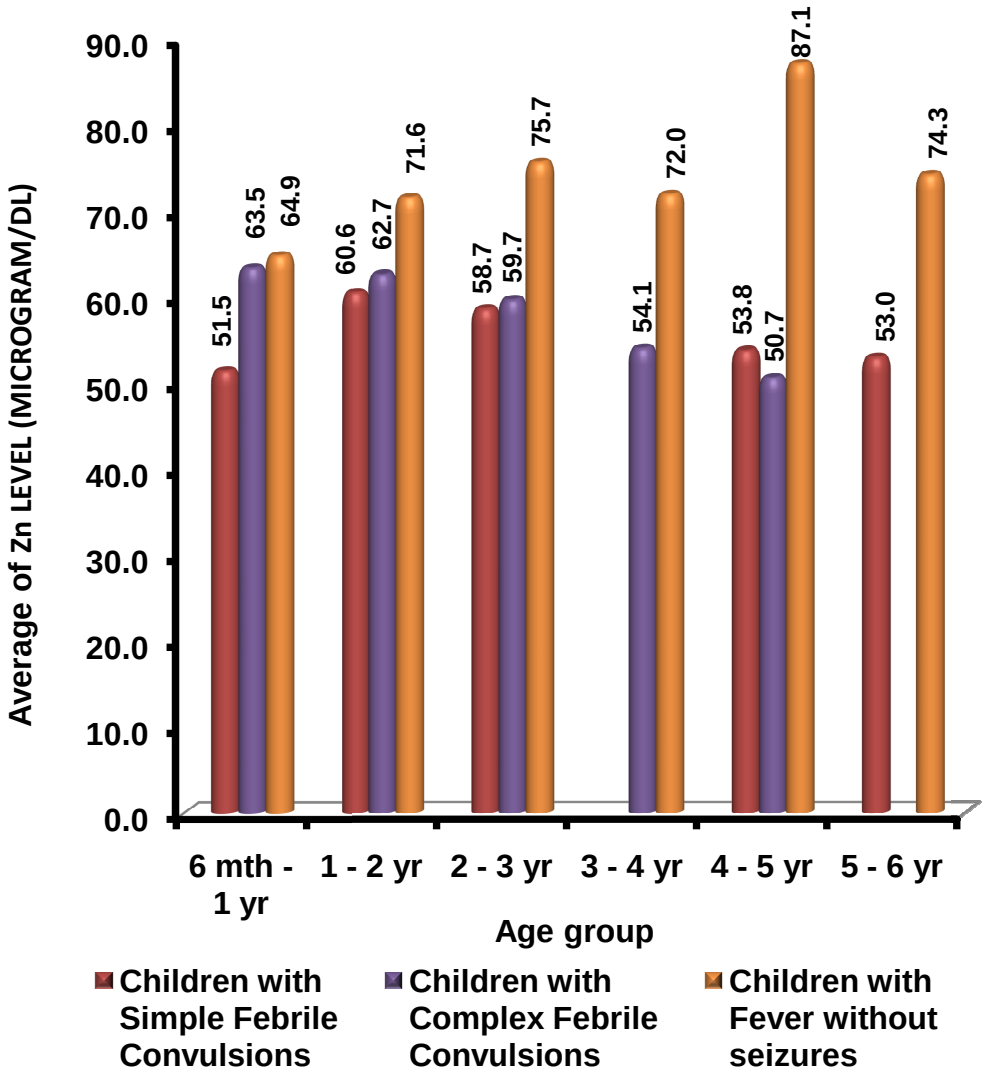
Thus there is a statistically significant difference in the serum zinc levels measured in the children with simple and complex febrile seizures in comparison to febrile children without seizures.

However, though serum zinc levels were found to be lower in simple febrile convulsions than complex febrile convulsions, statistically there was no significant difference between the two groups.

TABLE 17: AGE WISE DISTRIBUTION OF SERUM ZINC LEVELS (MICROGRAM/DL) IN THE THREE GROUPS

Age	Children with Simple Febrile Convulsions	Children with Complex Febrile Convulsions	Children with Fever without seizures	P-value
6 months – 1 yr	51.5	63.5	64.9	0.441
1 – 2 yrs	60.6	62.7	71.6	
2 – 3 yrs	58.7	59.7	75.7	
3 – 4 yrs	nil	54.1	72.0	
4 – 5 yrs	53.8	50.7	87.1	
5 – 6 yrs	53.0	nil	74.3	

FIG 16: AGE WISE DISTRIBUTION OF ZINC IN THREE GROUPS



The serum zinc levels are significantly lowered in all the age groups in children with simple febrile convulsions except in 1-2 yrs where the average is 60.6.

Among the children having atypical seizures serum zinc levels are significantly lowered in age groups of 2-3 years, 3-4 and 4-5 years

The average serum zinc levels are normal in all the age groups of children with fever without seizures from 6 months to 6 years.

Thus children with lower zinc levels at any age from 6 months to 6 years are prone to develop febrile convulsions.

TABLE 18: GENDER WISE DISTRIBUTION OF ZINC LEVELS

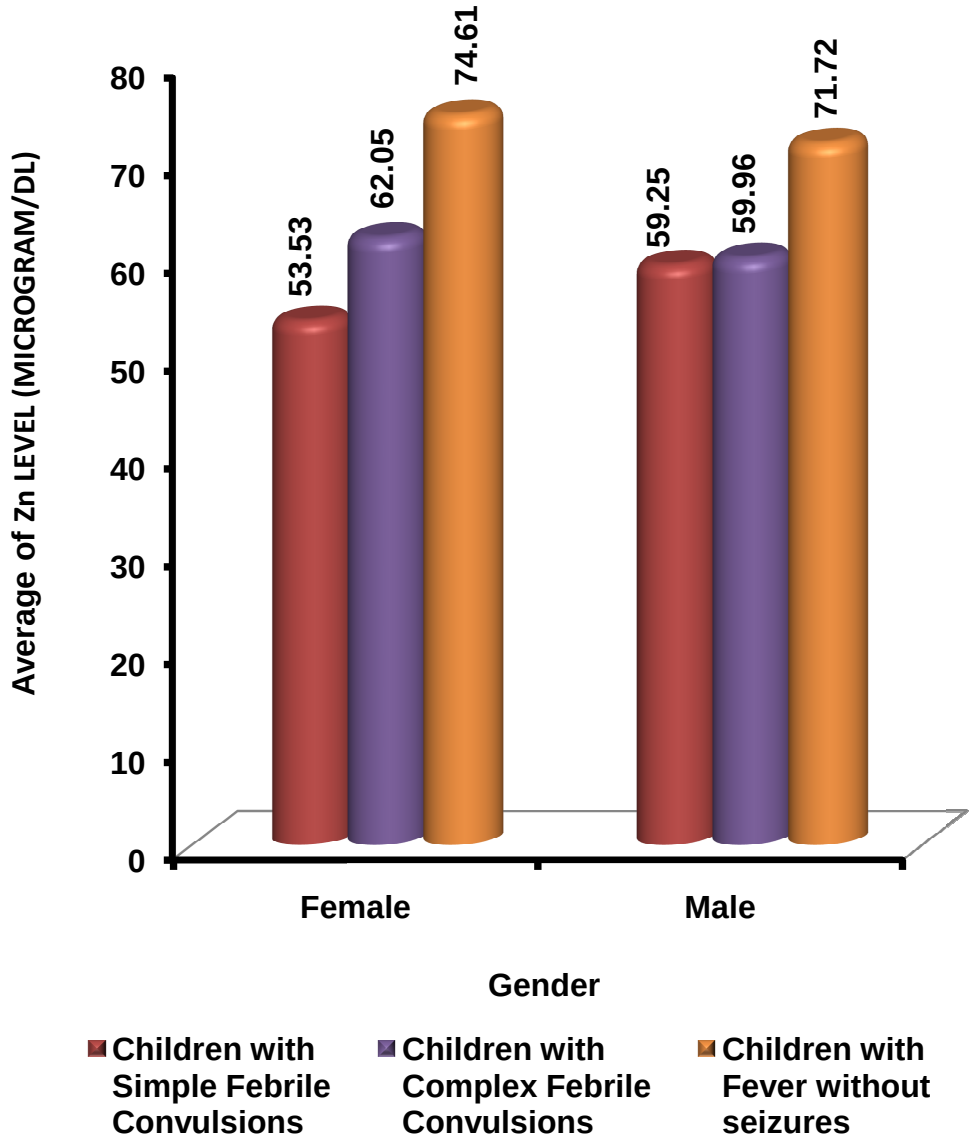
Gender	Children with Simple Febrile Convulsions	Children with Complex Febrile Convulsions	Children with Fever without seizures	P-value
Female	53.53	62.05	74.61	0.462
Male	59.25	59.96	71.72	

In the first group, male and female children had zinc levels of 53 and 59 mg/dl respectively

In the atypical convulsions group, the average zinc levels in males and female children were 62and 59 mg/dl respectively

In the fever group, male and females had zinc values of 74 and 71 mg/dl respectively.

FIG 17: GENDER WISE DISTRIBUTION OF ZINC LEVELS



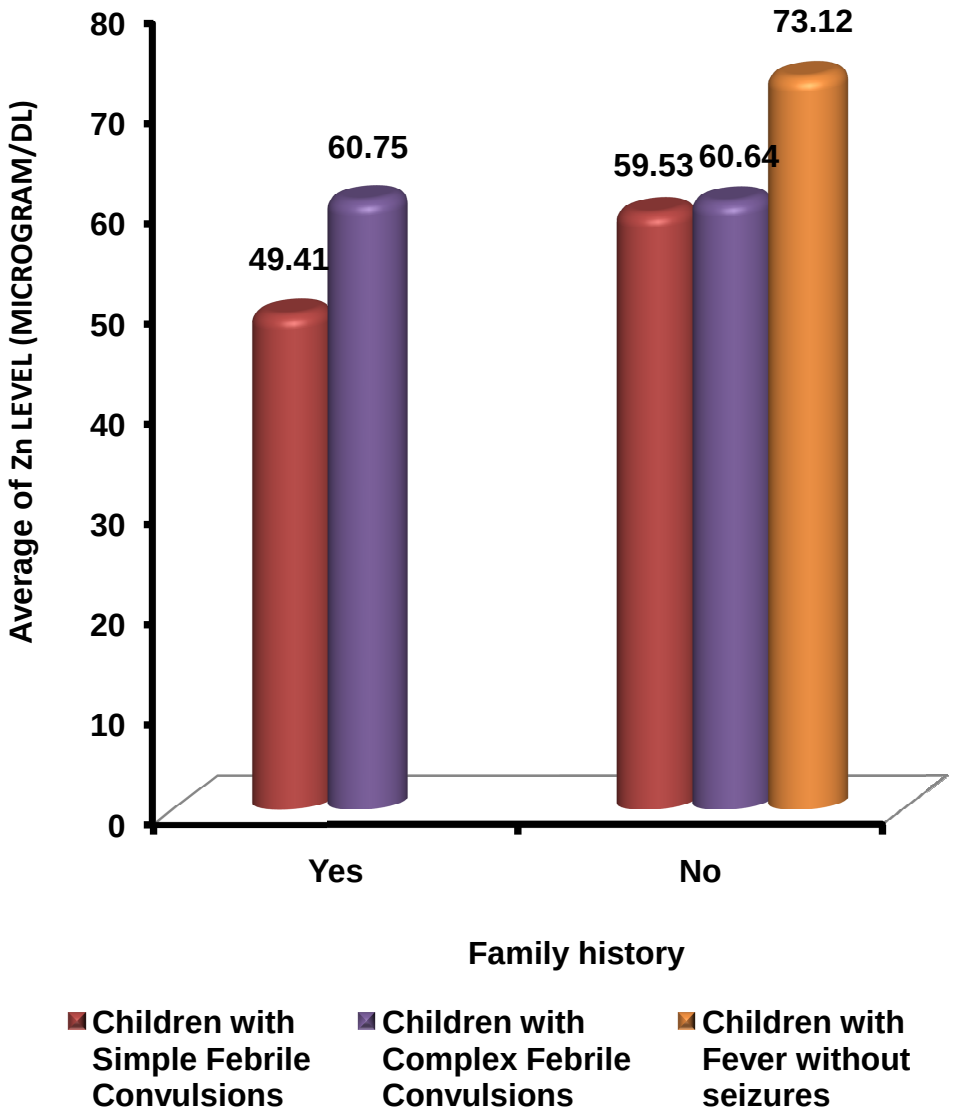
There was statistically no significant difference in the serum zinc levels based on gender distribution between the 3 groups

TABLE 19: COMPARISON OF ZINC VALUES WITH POSITIVE FAMILY HISTORY IN CHILDREN

Family history	Children with Simple Febrile Convulsions	Children with Complex Febrile Convulsions	Children with Fever without seizures	P-value
Yes	49.41	60.75	nil	0.206
No	59.53	60.64	73.12	

The average zinc levels in children with positive family history were 49 and 60 mg/dl in the children with simple and complex febrile convulsions respectively.

FIG 18: COMPARISON OF ZINC LEVELS IN CHILDREN WITH POSITIVE FAMILY HISTORY OF CONVULSIONS



There is no significant difference in the zinc values among the children with family history of convulsions.

Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean □ SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent.

Chi square is used to study the statistical difference if the comparison was between 2 parameters. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups.

Significant figures

+ Suggestive significance (P value: 0.05<P<0.10)

* Moderately significant (P value: 0.01<P □ 0.05)

** Strongly significant (P value : P□0.01)

Statistical Software

The Statistical software namely SAS 9.2, SPSS 11.5, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

DISCUSSION

Febrile seizure is a common neurologic problem occurring in children aged between 6 months to 6 years. The etiology of febrile seizure is unknown but genetic factors or electrolyte disturbances may have a role in its occurrence or recurrence. To date it is revealed that febrile seizures can be induced by several factors. There is a hypotheses that febrile seizures arise due to excitation of the neurons during brain growth. This correlates with the most common age group in which this entity occurs.

Gamma amino butyric acid is an important inhibitory neurotransmitter. Zinc has a regulatory effect on glutamic acid decarboxylase and the synthesis of GABA. Attempts have been made to identify predisposing risk factors like family history, metabolic disturbance (especially serum zinc, magnesium, glucose, calcium). This knowledge has a practical value in advising parents regarding recurrent convulsions.

This study was conducted to determine whether children with febrile seizures (simple and complex) had low serum zinc levels compared to febrile children without seizures. The three groups simple febrile convulsion, complex febrile convulsions and fever alone were comparable with respect to age, gender, and nutritional status.

AGE

Age is an important risk factor for the children to develop febrile convulsions.

The mean age of simple febrile convulsions was 24 months and complex febrile convulsions was 12 months in this study.

In the present study, 90% of patient among simple febrile convulsions were in the age group of 6months-2 years. 67% of patient among complex febrile convulsions were below 2 years and patients with fever alone below 2 years were 163%.

No significant difference were found in distribution of age in the study between the 3 groups.

In a study conducted by Samir S et al [83] the mean age was found to be 15/9-20 months.

In the study done by Lynette et al [84] he reported a mean age of 18 months.

In the another study done by Hartfield et al[85], he reported that maximum cases were in the age group less than 24 months and mean age was 17.9 months.

Manjunath et el[91] conducted a study which reported mean age of 24 months for simple febrile seizures and 26 months for complex febrile seizures.

Thus my study also showed similarity in the distribution of age in the three groups.

SEX DISTRIBUTION

In the present study there was male preponderance in all the three groups.

The male to female ratio is 1.7:1. Among children with simple febrile convulsions 28% were females and 72% were males. In cases with complex febrile convulsions 32% were females and 68 % were males. Among the fever group, 60% of the children were males and 40% were females.

The results of my study are supported by the following studies which showed similar results.

Hart field et al[85] showed a male preponderance of 57% in his study.

Leelakumari et al[86] had a male predominance of 50.65%.

In a study conducted by Samir S Shah et al [83] the male distribution was 57.3%.

Manjunath et al[91] showed a male to female ratio of 2:1 in his study

FAMILY HISTORY

Family history of convulsion has been attributed as one of the risk factors for recurrence of febrile seizures in various studies done earlier.

Siddique et al[87] reported an incidence of 30% in his study.

Saidal haque[88] in 1981 reported 20% of children with positive family history in his study.

Farwell[89] in 1994 reported positive family history in 29% of cases.

Manjunath et al[91] reported family history in 15% of cases.

A positive family history was present in 18% of children with simple febrile convulsion and 15% of children with complex febrile seizures in my study.

Thus the percentage in the present study is comparable to the other studies.

CAUSE OF FEVER ASSOCIATED WITH FEBRILE CONVULSIONS

Upper respiratory tract infection was found to be the most common triggering factor in studies done by Rantala et al in 1995 and Mahyaret al[90] in 2010.

Manjunath et al[91] showed upper respiratory infection as triggering illness in 72% and 82% of simple and complex febrile seizures.

In this study upper respiratory tract infection was found to be the triggering illness in 38% and 45% of simple and complex febrile seizures respectively.

Thus the percentage in our study is somewhat lesser when compared to the previous studies.

RANGE OF TEMPERATURE

In this present study 45% and 50% of children with simple and complex febrile convulsions recorded temperatures of 100 to 100.9 F.

Thus it gives a view that febrile seizure occur at lower temperatures in children with zinc deficiency.

SERUM ZINC

The mean serum zinc levels in the present study in simple and complex febrile convulsions and in fever alone without convulsions were 57 microgram/dl, 60 microgram/dl and 73microg/dl respectively.

Children with febrile convulsions both simple and complex have statistically significant low serum zinc levels when compared to children with fever alone without convulsions.

Children with fever alone did not show decrease in serum zinc level compared to other groups which is similar to findings of other studies.

Also there were no significant difference in serum zinc levels between simple and complex febrile convulsions.

Manjunath et al[91] compared 50 cases of simple and complex febrile seizures each with control which showed a significant low zinc values in seizure group ($p<0.002$).

Kumar L et al[65] in his study zinc values were significantly lower in cases compared to controls with p value<0.05.

Mollah et al[64] conducted a study comparing both serum and CSF zinc levels in febrile seizures with non convulsive fever group. He showed a statistically significant difference of p value<0.001.

Ganesh et al[79] from Chennai, Lee et al[93] and Amiri et al[92] also showed similar results.

The serum zinc levels did not show any significant correlation with age of onset, gender, family history and nutritional status in this present study. All previous studies have shown similar findings in this aspect.

As serum zinc concentration in any population is influenced by factors such as dietary pattern, vitamin A, vitamin D deficiency, zinc levels in the soil and water, further studies are needed in this aspect to identify the probable cause for this finding.

SUMMARY

A Cross Sectional Comparative study was done on 300 children during 6 month period at GMKMCH, SALEM.

Among them 60 children had simple febrile convulsions, 40 children had complex febrile convulsions and 200 cases had fever alone without convulsions. Serum zinc levels were measured in these patients.

This study was done to know the correlation between serum zinc levels and febrile convulsions (simple and complex).

- Majority of patients were in the age group below 2 years, comprising 90% and 69% in simple and complex febrile convulsions respectively.
- Among simple febrile convulsions male: female ratio was 2.5:1 and in complex febrile convulsions it was 2.0:1 and in the fever group it is 1.5:1.
- Upper Respiratory tract infection comprised about 38.2% and 45.0% of simple and complex febrile convulsions respectively while in fever alone 12%.
- Family history of febrile convulsions was positive in 18% and 15% of simple and complex febrile convulsions respectively.

- Majority of cases of simple and complex febrile convulsions had a temperature range of 100-100.9F and 101-101.9 F respectively.
- Only 22.2% and 36.4% had normal nutritional status whereas 50% of children with fever without seizures had normal nutrition.
- Serum zinc levels were low in 65% and 75% of simple and complex febrile convulsions respectively while in fever alone it was only 20% making it statistically significant. There was no statistical significance between simple and complex febrile convulsions.

CONCLUSION

Though the existence of febrile seizures has been known for centuries, the exact underlying mechanism still remains elusive to the researchers worldwide.

The current consensus understanding of which multifactorial etiology and many predisposing factors enthuses the researchers to explore more and more etiological and predisposing factors associated with febrile seizures.

The present study has shown that zinc deficiency is one of the predisposing factors for simple and complex febrile convulsions thereby making a small contribution to the medical literature by strongly establishing the relationship between zinc deficiency and febrile seizures.

Also the significant proportion of children (20%) in the group of fever without seizures in the study population is vulnerable to develop febrile seizures and needs zinc supplementation.

Future research should be directed towards the therapeutic trial of zinc supplementation and formulating the zinc treatment regimen including its dose and duration.

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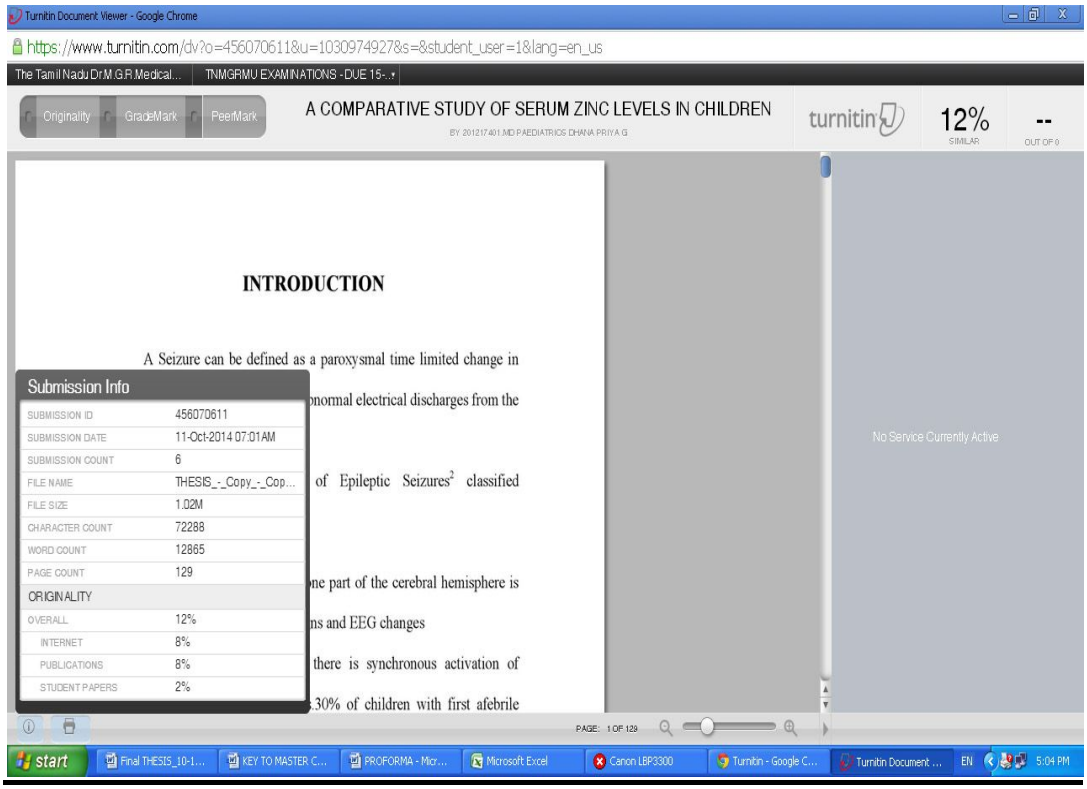
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INTRODUCTION
A Seizure can be defined as a paroxysmal time limited change in
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of Epileptic Seizures[2] classified
ne part of the cerebral hemisphere is
ns and EEG changes
there is synchronous activation of
30% of children with first afebrile
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